THE IMPACT OF ELECTRON-WITHDRAWING GROUPS ON THE REACTIVITY AND SOLUBILITY OF BENZYLOXYPYRIDNIUM SALTS

A THESIS

SUBMITTED TO THE GRADUATE SCHOOL

IN PARTIAL FULLFILLMENT OF THE REQUIREMENTS

FOR THE DEGREE

MASTERS OF SCIENCE

BY

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BALL STATE UNVIERSITY

MUNCIE, INDIANA

DECEMBER 2019

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Committee Approval

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Committee Chairperson	Date
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Committee Member	Date
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Committee Member	Date

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Dean of Graduate School	Date

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Abstract

Over the last decade, 2-benzyloxy-1-methylpyridinium triflate (BnOPT) has been found to be a highly effective reagent for the benzylation of alcohols and other nucleophiles. Benzylation using BnOPT is performed under relatively neutral conditions, as opposed to the more extreme pH's needed in traditional methods to synthesize benzyl ethers. The proposed mechanism for this benzylation occurs by an S_N1-like pathway in which BnOPT decomposes under a mild application of heat to form a benzyl cation which is subsequently captured by the nucleophilic alcohol. Based on this mechanism, a second generation of benzyloxypyridinium salts possessing electron-withdrawing groups on the pyridyl component have been designed as more efficient benzyl transfer reagents. The electron-withdrawing groups allow for benzyl cation formation at lower temperatures and/or shorter reaction times. A potential drawback to these derivatives is their increased unit cost resulting from the additional steps and time required to synthesize them, and their efficiency is limited given their one-time usage. This thesis will focus on the development and synthesis of a new benzoyl-substituted benzyloxypryridnium salt derivative designed to not only possess increased reactivity based on electronic effects, but also increased solubility in relatively non-polar solvents. This enhanced solubility should allow for more efficient molecule interaction and easier byproduct isolation. Future studies will focus on the recycling of the pyridone byproduct to regenerate the reactive salt to further increase the efficiency of these reagents. These new benzyloxypyridinium salt derivatives should allow for broader use and application of these reagents as mild benzylation reagents in the synthesis of complex and sensitive organic compounds.

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Chapter 1: Background

Chapter 2: Byproduct Isolation and Benzoyl Derivative Development

List of Abbreviations and Acronyms

Salts:

BnOPT: 2-Benzyloxy-1-methylpyridinium triflate

AMPT: 2-Allyloxy-1-methylpyridinium triflate

BnOLT:2-Benzyloxy-1-methyllepidine triflate

Solvents:

$PhCH_3$: Toluene

$PhCF_3$: α,α,α-Trifluorotoluene

EtOAc: Ethyl acetate

THF: Tetrahydrofuran

DCM: Dichloromethane

Reagents:

LAH: Lithium aluminum hydride

MeOTf: Methyl triflate

Cu(I)Cl: Copper (I) Chloride

$EtBr_2$: Ethylene Bromide

Bases:

MgO: Magnesium oxide

KOH: Potassium hydroxide

K_2CO_3: Potassium carbonate

Substrates:

PMB: Para-methoxybenzyl

EWG: Electron withdrawing group

Time:

h: Hours

min: Minutes

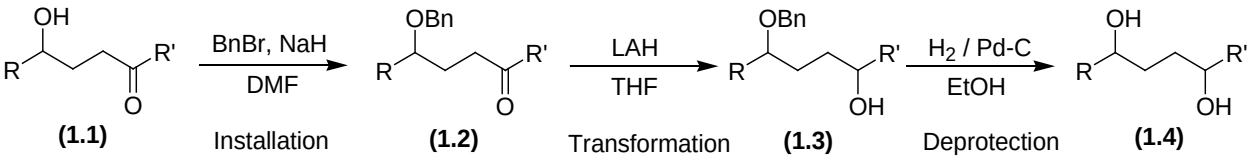
Chapter 1
Background

1.1 Protecting Groups

Modern organic chemistry allows for the synthesis of increasingly complex molecules with a variety of reactive functional groups. One of the primary challenges in complex molecule synthesis is controlling the selectivity of reactions to a particular functional group. Protecting groups are routinely used to control regio- and functional group selectivity in multistep synthesis.[1-2] Protecting groups are attached to a specific functional group to prevent alterations to it by rendering it inert during the subsequent steps of a synthesis.[1-2]

There are three phases to any protecting group scheme: Installation, transformations, and deprotection. The installation and deprotection steps are additional steps which do not move the total synthesis forward, so it is essential they are simple, selective, efficient, and high yielding. The intermediate transformation steps are where the protecting group blocks the reactivity of a particular function to prevent it from interfering in the desired transformation.

Scheme 1.1 Protection of an Alcohol



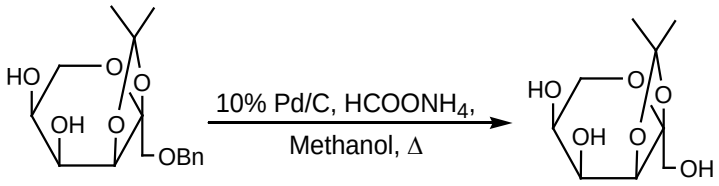
In the example protection group strategy in Scheme 1.1, the goal is to reduce the starting hydroxyketone (**1.1**) to the corresponding diol (**1.4**). The hydroxyl group in **1.1** has an acidic hydrogen

that could quench the reducing agent, LAH. The nucleophilic hydroxyl group could also attack the ketone to form cyclic hemi-acetal, which would limit the ability to reduce the ketone. To minimize these potential issues, a benzyl protecting group is added in the installation step to form a benzyl ether using benzyl bromide and sodium hydride. Now, the ketone can be reduced with LAH to the corresponding alcohol (**1.3**). The final step is the removal of the benzyl group by hydrogenolysis to deprotect the original alcohol and form the product diol (**1.4**).

1.2 Benzyl Ethers

Protecting groups are used in organic synthesis to block the reactivity of certain functional groups, and benzyl ethers have been used frequently as protecting groups for hydroxy groups. The popularity of this protection route is due to the robust stability of the benzyl group under a variety of reaction conditions including extreme pH conditions and high temperatures,[3] and its mild and selective removal at a relatively neutral pH.[4] On the other hand, other hydroxyl protecting groups, such as *t*-butyl ethers, are readily cleaved in the presence of strong base or even mildly acidic mediums. As a result, benzyl ethers serve as a popular choice for the protection of a hydroxyl group due to its broad versatility.[5]

Scheme 1.2: Deprotection of Alcohol [4]



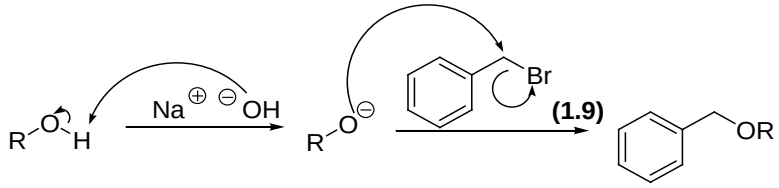
(1.5) **(1.6)** 96%

In Scheme 1.2, the benzyl ether on the carbohydrate (**1.5**) is successfully cleaved using catalytic hydrogenation consisting of 10% palladium on carbon and ammonium formate as a hydrogen source in hot methanol. This allows for removal of the benzyl group under relatively neutral, reductive conditions, and 96% yield of the alcohol (**1.6**) was obtained, while the acetonide group is left intact.[4] While benzyl

ethers are stable to a wide variety of reaction conditions, and are selectively removed under mild conditions, the traditional routes for the installation of benzyl ethers is potentially more problematic.

Historically, there are two primary routes to synthesize benzyl ethers: the Williamson ether synthesis (Scheme 1.3),[6] or through the usage of an acid-activated trichloroacetimidate (Scheme 1.4).[6-7] In the Williamson ether synthesis, Scheme 1.3, an alcohol (**1.7**) is first deprotonated by a strong base such as sodium hydride or sodium hydroxide to form an alkoxide (**1.8**). The electron rich alkoxide then performs a nucleophilic attack on an alkyl halide such as benzyl bromide (**1.9**) in an S_N2 reaction to form a benzyl ether (**1.10**).[6] This highly basic reaction has its limitations with complex substrates because of the potential for competitive reactions such as eliminations or nucleophilic attack on other electrophilic group, Scheme 1.3.[6, 8]

Scheme 1.3: Williamson Ether Synthesis[6]

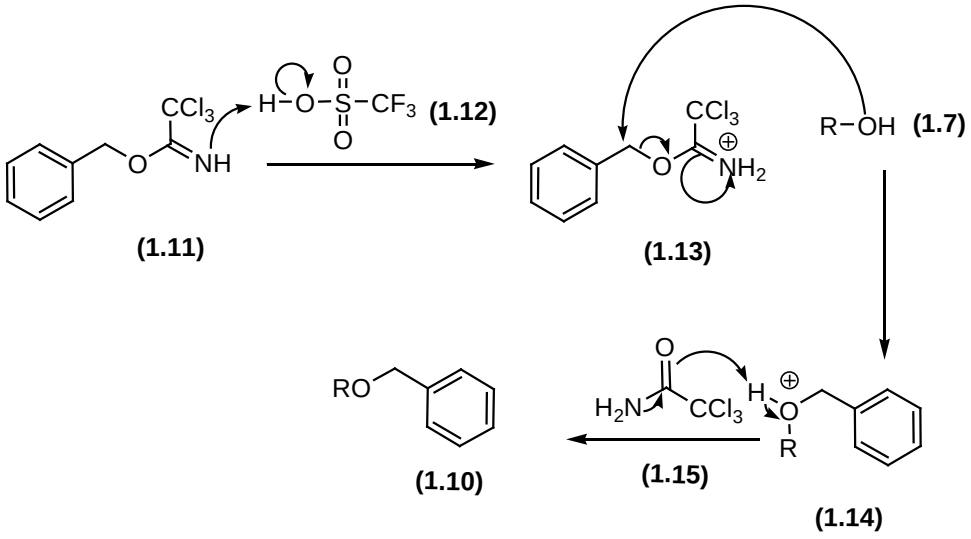


(1.7) **(1.8)** **(1.10)**

The second traditional method for generating benzyl ethers is the usage of an acid-activated trichloroacetimidate (**1.11**) as shown in Scheme 1.4. Activation of **1.11** occurs by protonation of the nitrogen atom of trichloroacetimidate by a strong acid, such as triflic acid (**1.12**). Subsequent nucleophilic attack by the alcohol (**1.7**) at the benzyl carbon yields the corresponding benzyl ether (**1.10**).[7] A major disadvantage of this method is its usage of triflic acid (**1.12**), which has an approximate pka of -15.[8] Even mildly basic functional groups can be protonated by the highly acidic (**1.12**), which can allow for an unwanted elimination or other side reactions to occur. Both traditional methods of benzyl ether synthesis, Schemes 1.3-4, have the potential for side reactions or decomposition to occur due to the extremely low or high pH's used, respectively. This limitation highlights the need for a benzyl

etherification method using more neutral conditions for molecules containing multiple sensitive functional groups.

Scheme 1.4: Synthesis of Benzyl Ether from Trichloroacetimidate[7]

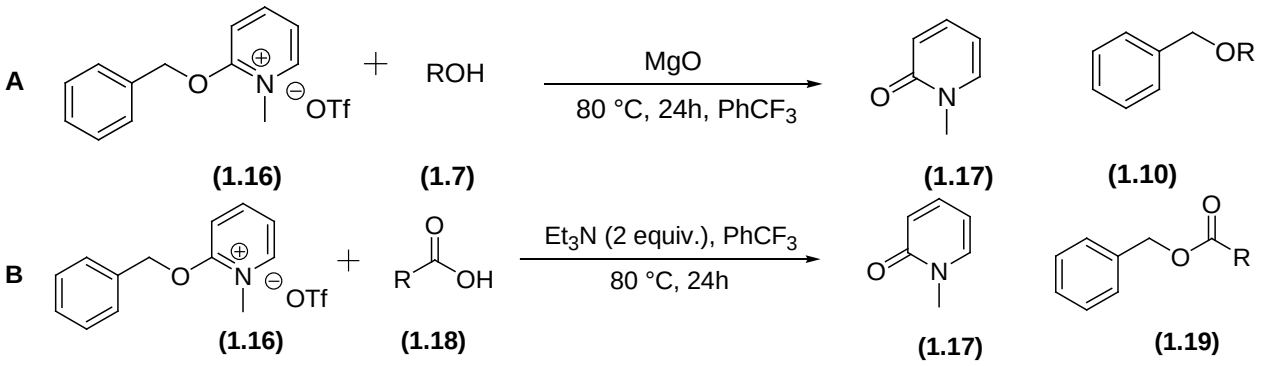


1.3 2-Benzyloxy-1-Methylpyridinium Triflate

Given the harsh conditions required in the classical methods (Scheme 1.3-1.4)[7, 9] of benzyl ether (**1.10**) formation, a new method which utilizes neutral conditions would be extremely advantageous in expanding the utility of benzyl ethers. 2-Benzyloxy-1-methylpyridinium triflate (BnOPT) (**1.16**), or Dudley's salt, was designed to enable the synthesis of benzyl ethers and esters under relatively neutral conditions. Specifically, **1.16** provides an electrophilic benzyl synthon which reacts with an alcohol[8] (**1.7**) or carboxylic acid[9] (**1.21**) to yield ethers (**1.10**) or esters (**1.19**), respectively. In the formation of ethers and esters, salt **1.16** and a substrate (**1.7** and **1.18**) are allowed to react at 80 °C in trifluorotoluene as shown below, Scheme 1.5 A-B. Magnesium oxide is included in the ether synthesis to serve as an acid scavenger, Scheme 1.5 A. On the other hand, Et_3N is used in the esterification procedure to activate the carboxylic acid (**1.18**) for benzylation in the formation of benzyl esters (**1.19**), Scheme 1.5 B. The second equivalent of Et_3N quenches any remaining benzyl cation formed in the reaction mixture to minimize

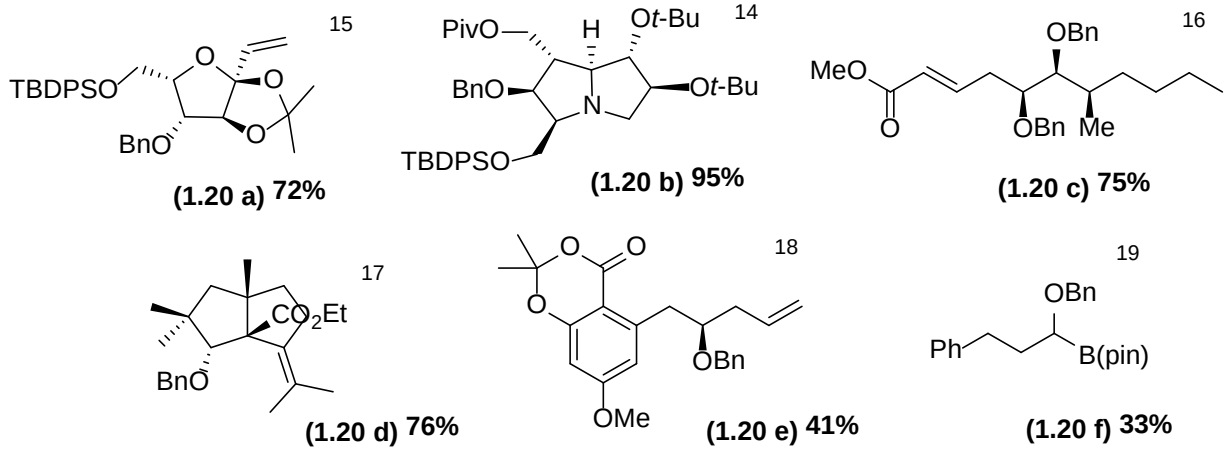
byproduct contamination. In both of these synthetic routes, the formed ether (**1.10**) or ester (**1.19**) was isolated by extraction using EtOAc, and the pyridine byproduct (**1.17**) is washed into water.[10-11]

Scheme 1.5: Synthesis of Ether using Dudley Salt[9, 12]



Based on the success of **1.16** as a mild and neutral benzylation reagent, many other studies have used **1.16** in the formation of benzyl ethers in complicated molecule synthesis. The compounds (**1.23 a-f**) synthesized in these studies contained functional groups that would be altered by the conditions of Williamson ether synthesis or acid activated tricholoacetimidate such as *t*-butyl ethers (**1.23 b**), *t*-butyl diphenyl silyl ethers (**1.20 a and b**), esters (**1.20 b-d**), and acetals (**1.20 a**).[13-18] In the benzylation of alcohols with chiral centers was found to occur without racemization at the alcohol's chiral center (**1.20 d-f**), avoiding an unwanted mixture of isomers in a product, Figure 1.1.[13-18]

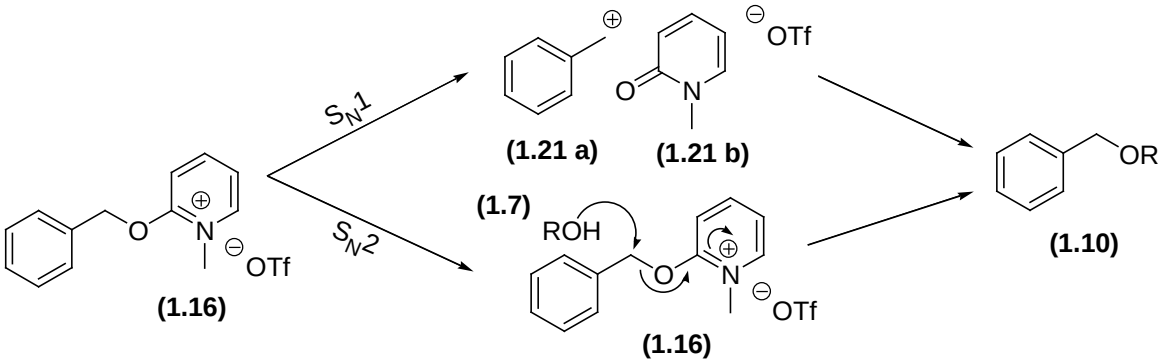
Figure 1.1: Benzyl Ethers Produced by BnOPT [10, 13-15, 17-20]



1.4 Mechanism of Benzyl Transfer with BnOPT

In the case of BnOPT, there are two possible extremes for the mechanism of nucleophilic substitution, S_N1 or S_N2, Scheme 1.6. In the S_N1 pathway, **1.16** decomposes to provide a benzyl carbocation (**1.21 a**) and pyridone (**1.24 b**). The alcohol (**1.7**) can subsequently attack the benzyl carbocation (**1.21 a**) followed by deprotonation to produce the benzyl ether product (**1.10**). The second route follows a S_N2 pathway, where the alcohol (**1.7**) directly attacks **1.16** and displaces the pyridone leaving group followed by deprotonation to produce **1.10**.[21]

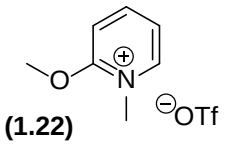
Scheme 1.6: S_N1 and S_N2 Pathways[21]



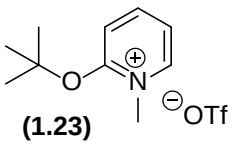
[a.] Scheme 1.6 suggests the mechanism is either one of the two extremes, either S_N1 or S_N2; however, there are studies that suggest BnOPT (**1.16**) does not react strictly S_N1 and S_N2, but in a spectrum of either S_N1-like or S_N2-like.

In order to take full advantage of the potential functionality of pyridinium salts, two new aryl pyridyl derivatives, the methyl (**1.22**) and *t*-butyl (**1.23**), were developed in order to help elucidate the mechanism of electrophilic transfer. These two substrates were chosen specifically because they strictly favor either an S_N1 or S_N2 mechanism because of varying carbocation stability and steric hinderance of the aryl group, Figure 1.2.

Figure 1.2: Aryl Pyridyl Derivatives



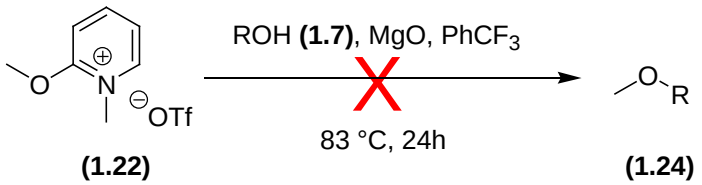
(1.22)



(1.23)

To test the likelihood of an S_N2-like mechanism, the benzyl group on **1.16** was replaced with a methyl group (**1.22**), Scheme 1.7. The methyl group was chosen because of its lack of steric hindrance at the α-carbon, making it an ideal S_N2 candidate. On the other hand, the resultant methyl cation would be highly unstable, making it a very poor S_N1 candidate. The derivative 2-methoxy-1-methylpyridinium triflate (**1.22**) was heated at 80 °C for 24h in the presence of an alcohol, but the reaction did not generate any of the predicted methyl ether product (**1.24**), Scheme 1.7. Since the derivative designed to favor an S_N2-pathway was completely unreactive towards electrophilic transfer, by analogy BnOPT may also disfavor the S_N2 mechanism.[11]

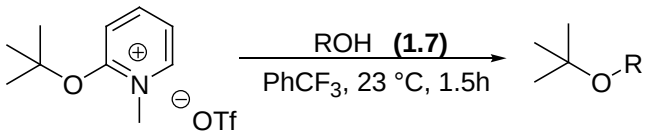
Scheme 1.7: Failed Formation of Methyl Ethers using 2-Methoxy-1-Methylpyridinium Triflate[11]



(1.22) **(1.24)**

To determine if an S_N1-like mechanism is favored, the benzyl group of BnOPT (**1.16**) was replaced with a *t*-butyl group producing 2-*t*-butoxy-1-methylpyridinium triflate (**1.23**), Scheme 1.8.[22] The *t*-butyl group is an ideal S_N1 electrophile, due to the greater stability of the resultant tertiary carbocation. On the other hand, the significant steric hinderance of the *t*-butyl group prevents the backside nucleophilic attack that is required for an S_N2 reaction. When **1.23** was allowed to stir with an alcohol, the resultant *t*-butyl ether was formed readily. In fact, the conditions required to form *t*-butyl ethers were significantly milder than the original conditions with BnOPT. The combined results of these two new derivatives provide support that oxypyridinium salts generally transfer an electrophilic component *via* a 2-step process in which the salt decomposes to a carbocation, followed by nucleophilic trapping. The implementation of the *t*-butyl group also serves to expand the utility of pyridinium salts, because *t*-butyl ethers have been traditionally synthesized using isobutylene gas and acidic conditions, Scheme 1.8.[22-23]

Scheme 1.8: Formation of *t*-Butyl Ethers using 2-*t*-Butoxy-1-Methylpyridinium Triflate[22]

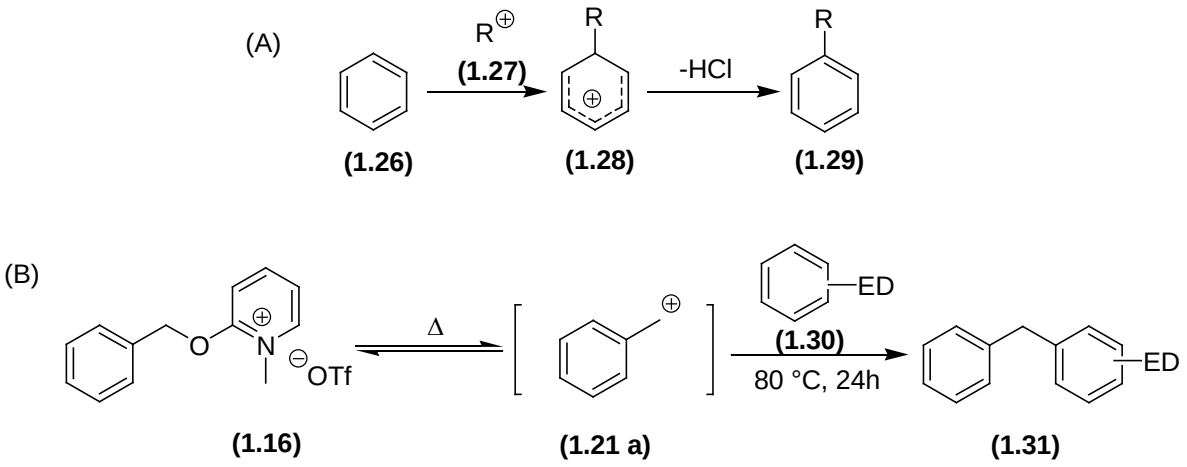


(1.23) **(1.25)**

10 alcohols (52-91%)

These reactions reached completion after 1.5h at 23 °C as opposed to the 24h at 83 °C for **1.16**. The significantly shorter reaction time and lower temperature needed to complete the reaction suggest a more stable transition state in the rate determining step, and overall lower activation energy for the formation of the *t*-butyl ether (**1.25**).[22] These findings imply an S_N1 mechanism is generally favored by oxypyridinium salts, but specific evidence for the mechanism of benzyl ether synthesis using salt **1.16** was not provided by these experiments. Therefore, an additional study using BnOPT in Friedel-Crafts alkylations was performed to determine if an S_N1-like mechanism was feasible for BnOPT.

Scheme 1.9: Friedel-Crafts Benzylation with Classical Method (A) and with BnOPT (B)[24-25]

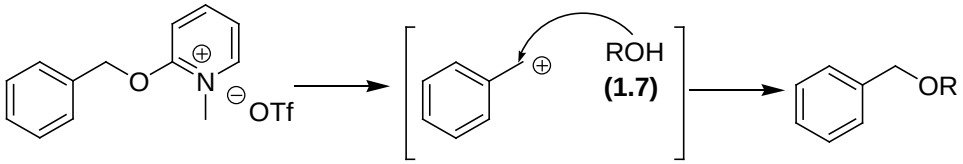


7 examples, (43-100%)

BnOPT was allowed to stir with mild heating in aromatic solvents to determine if Friedel-Crafts type reactions would take place. Carbocation formation is an essential step in Friedel-Crafts alkylation. In the traditional Friedel-Crafts alkylation, a carbocation (**1.27**) would be produced from the reaction of

a benzyl halide and a Lewis acid to allow for a nucleophilic attack by an electron-rich arene to occur, Scheme 1.9 A.[24-25] When salt **1.16** is used in this reaction, the salt decomposes under the application of heat to produce a benzyl carbocation (**1.21 a**), which an electron rich arene (**1.30**), such as toluene or anisole, can attack via nucleophilic substitution.[24] Given the success of **1.16** in substituting a variety of arenes, including the less-activated and even deactivated substrates such as benzene and bromobenzene respectively, a S_N1-like mechanism is supported, Scheme 1.9 B.[24] With this study and the investigation into the aryl pyridyl derivatives (**1.22** and **1.23**), a significant amount of evidence supporting an S_N1-like mechanism for **1.10** formation using **1.16** has been found. Specifically, it has been proposed based on these experiments that **1.16** will decompose under the application of heat to generate benzyl cation (**1.21 a**), followed by nucleophilic trapping with an alcohol (**1.7**) producing **1.10** as seen in Scheme 1.10.[10-11]

Scheme 1.10: Benzyl Ether Formation using BnOPT[10-11]



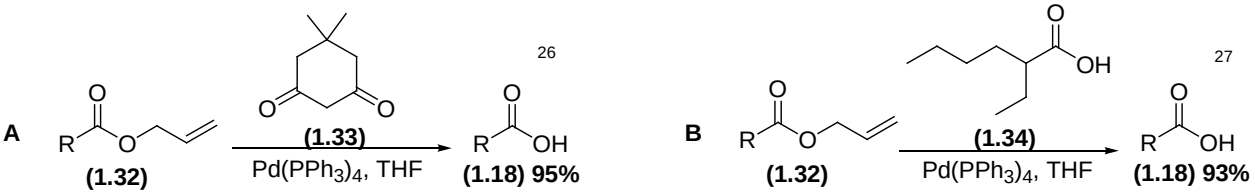
(1.16) **(1.21 a)** **(1.10)**

Evidence was observed with these studies that salts that would generate extremely unstable carbocations, such as the methoxy derivative (**1.22**), were unreactive with alcohols, Scheme 1.7. On the other hand, salts that would generate stable carbocations, such as the *t*-butyl (**1.23**) and benzyl derivatives (**1.16**), yielded the corresponding ether products when reacted with alcohols. However, the threshold of cation stability between methyl and benzyl is still in question. To both examine this mechanistic threshold and expand the utility of oxy pyridinium salts, the allyloxy group was introduced in a new salt derivative.[26]

1.5 Usage of the Allyl Group

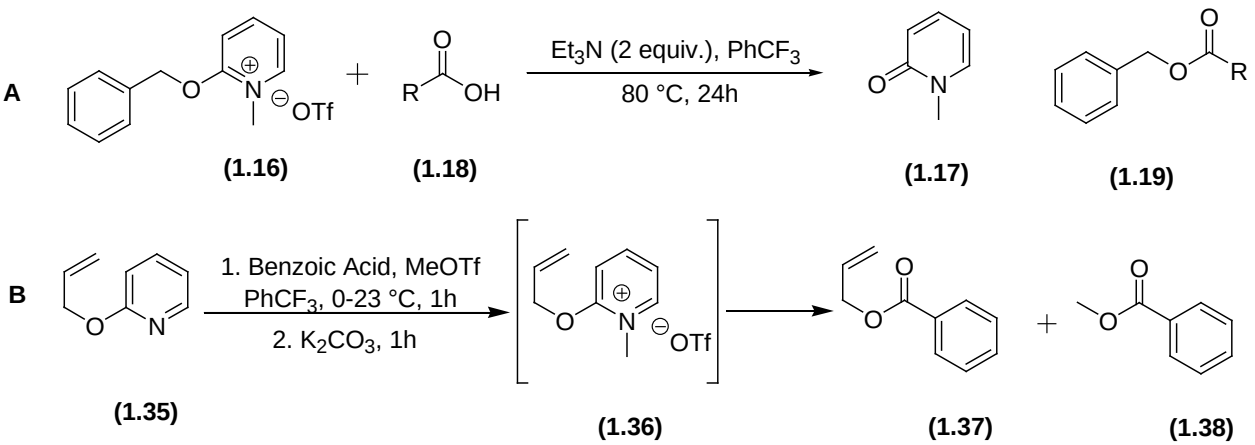
The allyl ester functional group is a very popular protecting group for carboxylic acids, because like the benzyl group, the allyl group is generally unaffected by either basic or acidic conditions.[2] It is also mildly and selectively removed using palladium/triphenylphosphine complexes combined with either dimedone (**A**) or ethylhexanoic acid (**B**) to form the respective carboxylic acid (**1.18**) in high yields, Scheme 1.11.[27-28] Therefore, it seemed that an allyloxy pyridinium salt derivative would make a good target for expanding the utility of these reagents.

Scheme 1.11: Palladium-Catalyzed Cleavage of Allyl Group with A) Dimedone and B) 2-Ethylhexanoic Acid[26-27]



Allyl transfer to carboxylic acids *via* 2-allyloxy-1-methylpyridinium triflate (AMPT) (**1.36**) is possible, but required an *in situ* formation and reaction.[25] This was due to salt **1.36** having an amorphous composition which made its isolation complicated, Scheme 1.12 B.[21, 26]

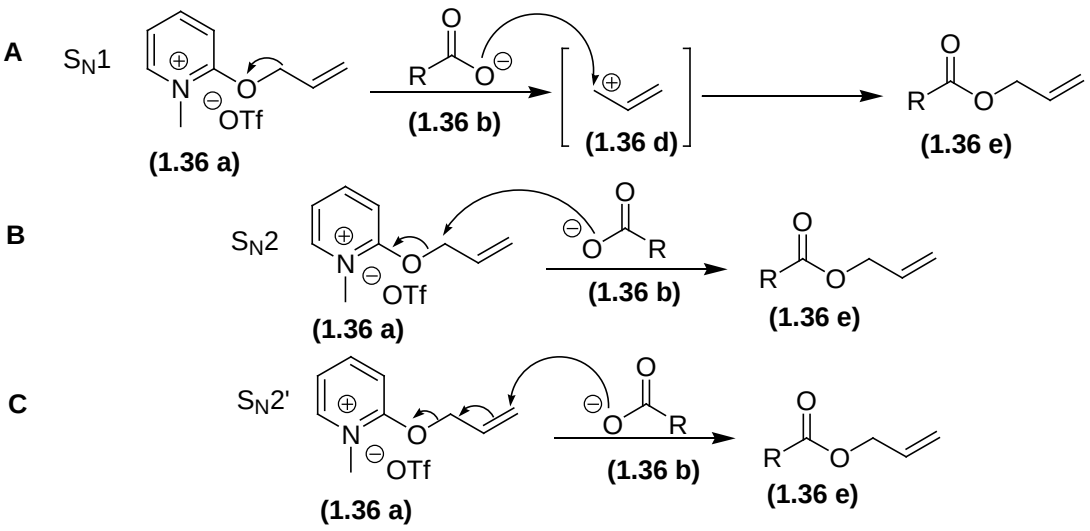
Scheme 1.12: Synthesis of Benzyl (A) and Allyl Ester (B)[21, 26]



The reaction of carboxylic acids with salt **1.36** showed a variety of differences when compared to the same reaction with BnOPT. The reaction time for the formation of allyl esters (**1.37**) was significantly shorter than the formation of benzyl esters requiring 1h (**B**) instead of 24h (**A**), Scheme 1.12. A stronger base, K_2CO_3, was also needed for the complete consumption of **1.36.** A methyl ester byproduct (**1.38**) was also found to have formed with **1.37**, Scheme 1.12 B. These differences in the reaction conditions and outcomes are clues that the mechanism of electrophilic transfer might be different for these allylations.

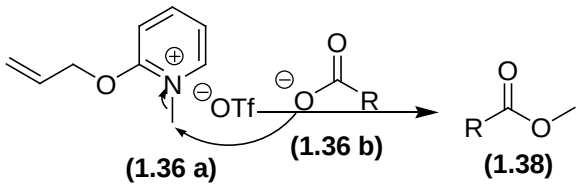
Several possible mechanisms based on the experimental conditions were possible for the synthesis of allyl esters using **1.36 a**. An S_N1 mechanism for **1.36 a** would follow a similar pathway as the BnOPT with **1.36 a** decomposing to form the allyl cation (**1.36 c**), and the carboxylate anion (**1.36 b**) would perform a nucleophilic attack forming the allyl ester (**1.36 d**), Figure 1.4 a. Regarding an S_N2 mechanism for the formation of **1.36 d**, there are two proposed pathways. In one pathway, the nucleophilic attack would occur internally, Figure 1.4 b**,** where **1.36 b** attacks to cause a single bond cleavage to form the **1.36 d**, Figure 1.4 b. In the other S_N2 pathway, **1.36 b** attacks the terminal end of the allyl substrate to cause a series in bond cleavage to form **1.36 d**. The methyl ester byproduct is expected to be formed by an S_N2 mechanism where **1.36 b** directly attacks the methyl group on **1.36 a**, Figure 1.4 D.[9]

Figure 1.3: Potential Mechanisms for Allyl Ester Formation[21]



The finding of **1.38** in allyl esterification was significant, because this byproduct could only be produced by an S_N2 mechanism. **1.38** was not observed in the benzyl esterification, which has been predicted as having an S_N1-like mechanism.[24] Therefore, the formation of **1.38** provides evidence of a potential competition between S_N1 and S_N2 mechanism for allyl esterification**.** In the synthesis of **1.38**, *N*-methyl group on an undecomposed salt (**1.36 a**) would be attacked by the carboxylate anion (**1.36 b**) to form the **1.36 c**, Figure 1.3.

Figure 1.4: Formation of Methyl Ester Byproduct

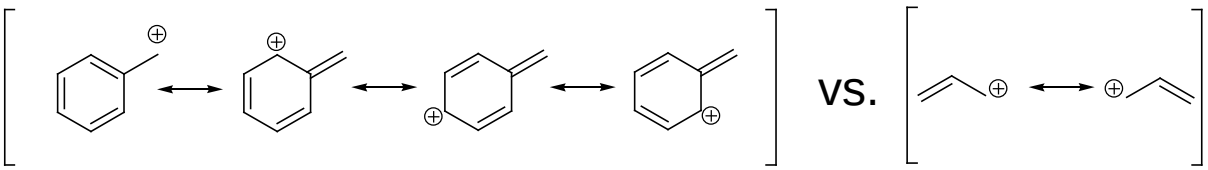


Additional evidence was provided for a competition between S_N1 and S_N2 mechanisms through the requirement for a stronger base, K_2CO_3, to achieve reaction completion. The stronger base would result in a greater nucleophilicity of the carboxylate anion to enable a nucleophilic attack on undecomposed **1.36 a**. This decomposition of **1.36 a** may not occur as readily on its own, due to the resultant allyl cation

having less resonance stabilization than the corresponding benzyl cation. Therefore, the extended stability of **1.36 a** could allow for a competitive nucleophilic attack of the carboxylate. The difference in reaction time between the allyl and benzyl esterification also suggest a higher potential for competition between S_N1 and S_N2 mechanisms. The benzyl esterification *via* BnOPT, proposed to proceed through an S_N1-like mechanism, occurred much slower than the allyl esterification. The S_N1 mechanism is typically slower than the S_N2 mechanism due to the lack of a driving force in the mechanism. The differences in time between the two esterification could suggest a higher potential for competition between S_N1 and S_N2 mechanisms for allylation using **1.36 a**.

The exact mechanism of **1.36** is currently unknown, but several mechanisms were proposed based on evidence of competition occurring between S_N1 and S_N2 mechanisms **1.36**'s reaction conditions. These reaction conditions result from the stability of the allyl group cation (**1.39 b**). The allyl cation's (**1.39 b**) stability makes it slightly more likely to undergo an S_N2 mechanism as opposed to the benzyl cation (**1.39 a**), due to the limited conjugation the ally group (**1.39 b**). This limited conjugation makes the allyl cation (**1.39 b**) less electrophilic than the benzyl cation, and therefore, more difficult to form. A mechanistic threshold in terms of what carbocations can be provided by pyridinium salts can be examined using the allyl cation as it does approach a S_N2-like substrate. The exact mechanism of the allyl transfer is unknown, but based on the evidence provided the nucleophile may be involved in the rate determining of the reaction or multiple mechanism may be occurring simultaneously, Figure 1.5.[22]

Figure 1.5: Difference in Benzyl and Allyl Resonance Contributors[22]



(1.39 a) **(1.39 b)**

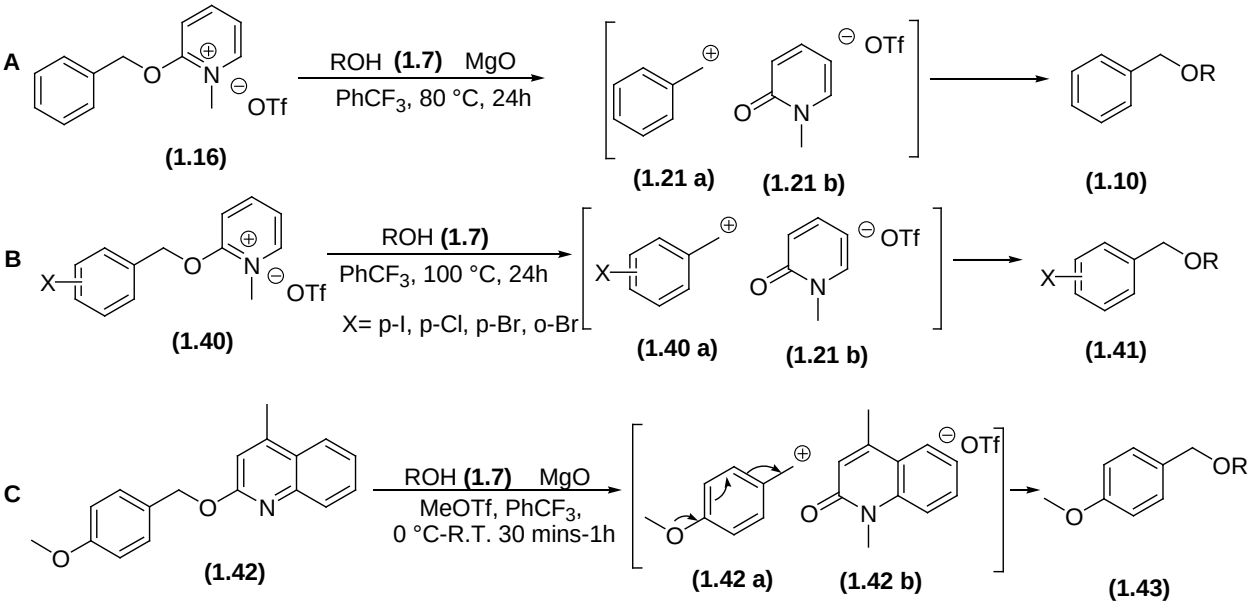
Allyl esterification was performed efficiently using **1.36**, but the formation of allyl ethers was not as successful. This was due to the need of a strong base for the synthesis of allyl ethers and using a strong base would not allow for neutral conditions but would instead be more like that of the Williamson ether synthesis.

Evidence was seen of pyridinium salts favoring an S_N1 mechanism with the usage of the t-butyl group[22] and Friedel-Crafts study[24], but evidence of a possible S_N2 mechanism was observed with **1.36** through the reaction conditions and products (**1.37** and **1.38**) formed. Both mechanisms could be enhanced by altering the reactivity of pyridinium salts, and this was accomplished in several derivatives. This series of derivatives not only expands the range of transferable electrophiles by this methodology, but also highlights differences in reactivity of the salts as the electron-density of the benzyl component changes.

1.6 Substituted Benzyl Derivatives

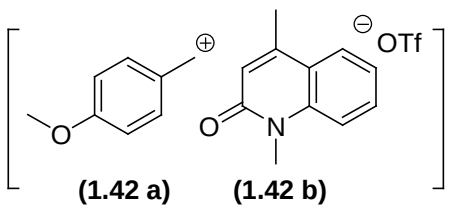
The benzyl group of BnOPT has been successfully replaced with the *t*-butyl and allyl group in studies examining the mechanism of oxypyridinium salts,[21-22, 26] but other carbocation substrates that can tune the reactivity of BnOPT by altering electron their electron density have been used as well. These substrates, including various halobenzyls (**1.42**)[29] and para-methoxybenzyl (PMB) (**1.44**),[30] were found to impact the time and temperature required for an electrophilic transfer reaction by either donating or withdrawing electrons from the benzyl group, Scheme 1.13.

Scheme 1.13: Substituted Benzyl Groups Compared to Benzyl Group



The halobenzyl derivatives (**1.41**) possess a similar structure to benzyl groups, except for an additional halogen substituent on the benzyl ring which causes mild deactivation by induction.[28] The electron-withdrawal *via* induction exceeds electron-donation *via* resonance due to the poor p-orbital overlap of the halogen atom with the aromatic carbons. This deactivation leads to a higher temperature required for the synthesis of halobenzyl ethers (**1.41**) (100 °C) compared to benzyl ethers (**1.10**), (80 °C) Scheme 1.13 B. The opposite effect is observed in the PMB derivative (**1.42**) using a lepidyl species in place of the pyridyl section. The para-methoxy group readily donates electrons into the ring via resonance making the resultant cation (**1.42 a**) more stable than BnOPT's (**1.21 a**). In fact, an *in situ* methylation and reaction with an alcohol (**1.10**) were required for the PMB derivative, because the ether (**1.42**) decomposes upon methylation at room temperature.

Figure 1.6: Anion Cation Pair

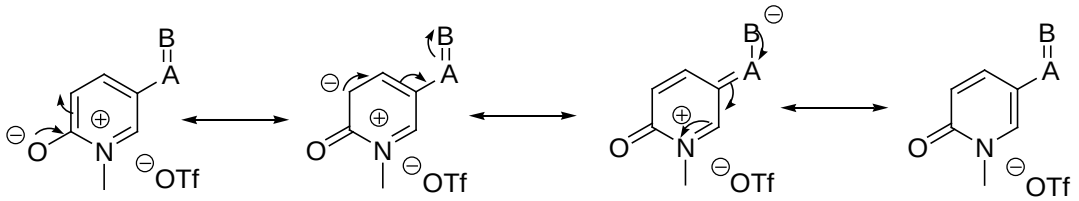


A trend is observed with the reactivity of these derivatives (**1.40** and **1.42**) as the varying functional groups have been shown to either enhance or lower the reactivity of a salt by altering the overall stability of the formed carbocation (**1.40 a** and **1.42 a**). As seen with the para-methoxy derivative (**1.42**), if the carbocation is stabilized by the functional group, the salt is expected to decompose more readily at a lower temperature and/or shorter time than BnOPT (**1.16**). A drawback to this altered reactivity is limited to the specific electrophilic group present within the salt (**1.42 a**), and therefore this tuned reactivity cannot be applied to other electrophiles. On the other hand, if the pyridyl section were altered electronically, fine-tuning the reactivity of the salt would be independent of the electrophile transferred. Specifically, electron withdrawing groups (EWG's) may be added to the pyridyl section of BnOPT (**1.21 b**) to allow for benzyl transfer reactions at more mild conditions.

1.7 Pyridyl Electron Withdrawing Groups

To enhance the reactivity of BnOPT, an electron withdrawing group was added to the pyridyl section of a salt. As a result, carbocation formation was expected to occur under more mild conditions than the original BnOPT salt. These mild conditions result from the EWG stabilizing the resulting pyridone anion (**1.44 a-d**) making it a more reactive leaving group, Figure 1.7.[31]

Figure 1.7: Predicted Mechanism for Electron Withdrawing Group Derivative[31]

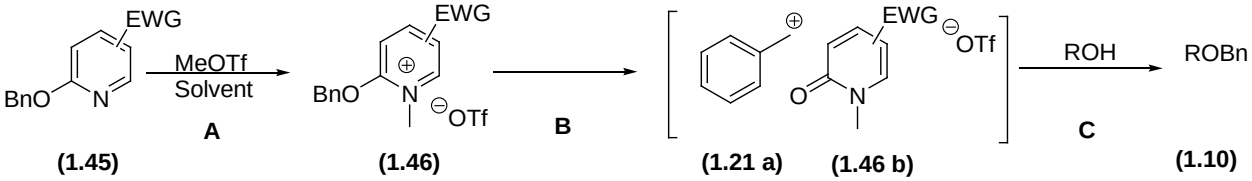


(1.44 a) **(1.44 b)** **(1.44 c)** **(1.44 d)**

The EWG's selected were positioned on the third and fifth positions on the pyridyl section as opposed to the second and fourth positions, because electron-withdrawal due to resonance could be maximized at

these positions. The groups covered ranged from weak to strong with regards to electron-withdrawing capability, and there were significant differences in the conditions for methylation and benzylation between the EWG derivatives (**entries 2-6**) and BnOPT based on the strength of the EWG, Table 1.1.[31]

Table 1.1: Usage of Electron Withdrawing Group Derivatives[31]



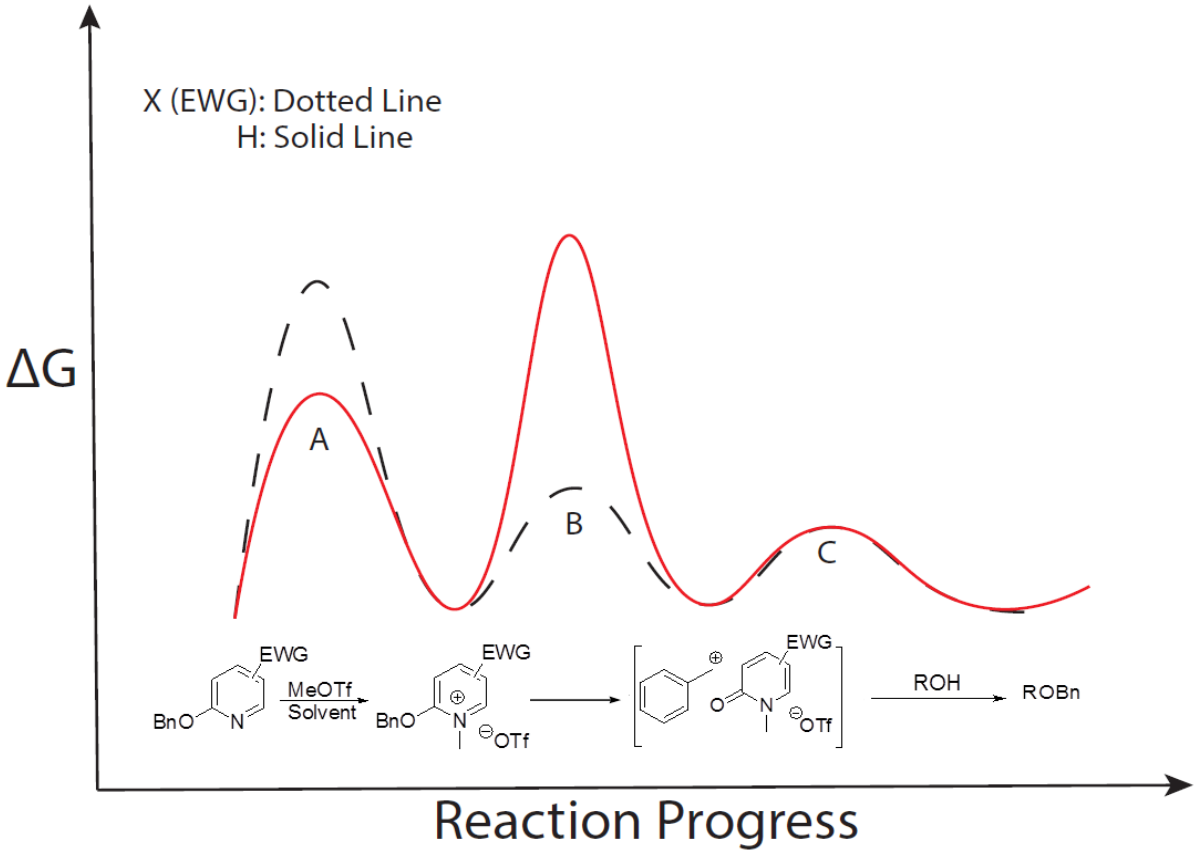
Entry	EWG	Temp (°C)/ Time (A)	Yield % (**1.46**)	Temp (°C)/ Time (B)	Yield % (**1.10**)
1	H	0 (1h)	99	80 (24h)	93
2	5-Cl	23 (5h)	92	60 (24h)	83
3	5-CN	50 (18h)	In situ	50 (18h)	39
4	5-CF_3	40 (18h)	In situ	40 (18h)	55
5	3-CF_3	45 (72h)	In situ	45 (72h)	56
6	5-NO_2	40	In situ	40	55

Both the time and temperature required for complete methylation of the derivatives (**1.45**) (entries 2-6 A) was significantly higher in comparison to BnOPT (entry 1). The 5-chloro derivative (entry 2) was isolated after 5h at 23 °C to obtain a 92%. A benzylation reaction using this derivative required a lower temperature of 60 °C to reach completion in 24h. Enhanced reactivity was provided with this derivative, but probably not enough to make a practical impact in the reaction conditions. As the strength of the EWG was significantly increased (entries 3-6) the salts (**1.46**) would begin decomposing immediately upon methylation (step **A**). As a result, *in situ* formation and benzylation reaction were required for these derivatives. The longer time needed for methylation of 18h to 72h for these derivatives (**1.45**), entries 3-6, created an additional complication with the possibility of methylation of the alcohol instead. This results from the pyridyl nitrogen on **1.45** having a similar nucleophilicity to the oxygen of the alcohol, due to the EWG located on **1.45**. These complications lead to need for a balance

between the activation energies of methylation and decomposition to increase the efficiency of using EWG derivatives.

The energy required for the methylation (transition state **A**) of strong EWG derivatives exceeds the energy needed for their decomposition (**B**), and therefore decomposition (**B**) will occur immediately upon methylation (**A**), Figure 1.8. This leads to a series of complications previously mentioned, but to counter act these a balance is needed between the energy required for methylation (**A**) and decomposition (**B**). Specifically, the conditions of methylation (**A**) would need less strenuous conditions by having a lower required temperature, while a higher temperature would be required for decomposition (**B**). This temperature would be less than what is required to decompose BnOPT as an EWG would provide enhanced reactivity. To obtain this balance in formation and decomposition energies, a set of derivatives using moderate EWG's were created to allow for benzylation at a faster rate than weak EWG derivatives, but not to the extent of requiring in situ conditions like the strong EWG derivatives.

Figure 1.8: Energy Differences between EWG Derivatives and BnOPT

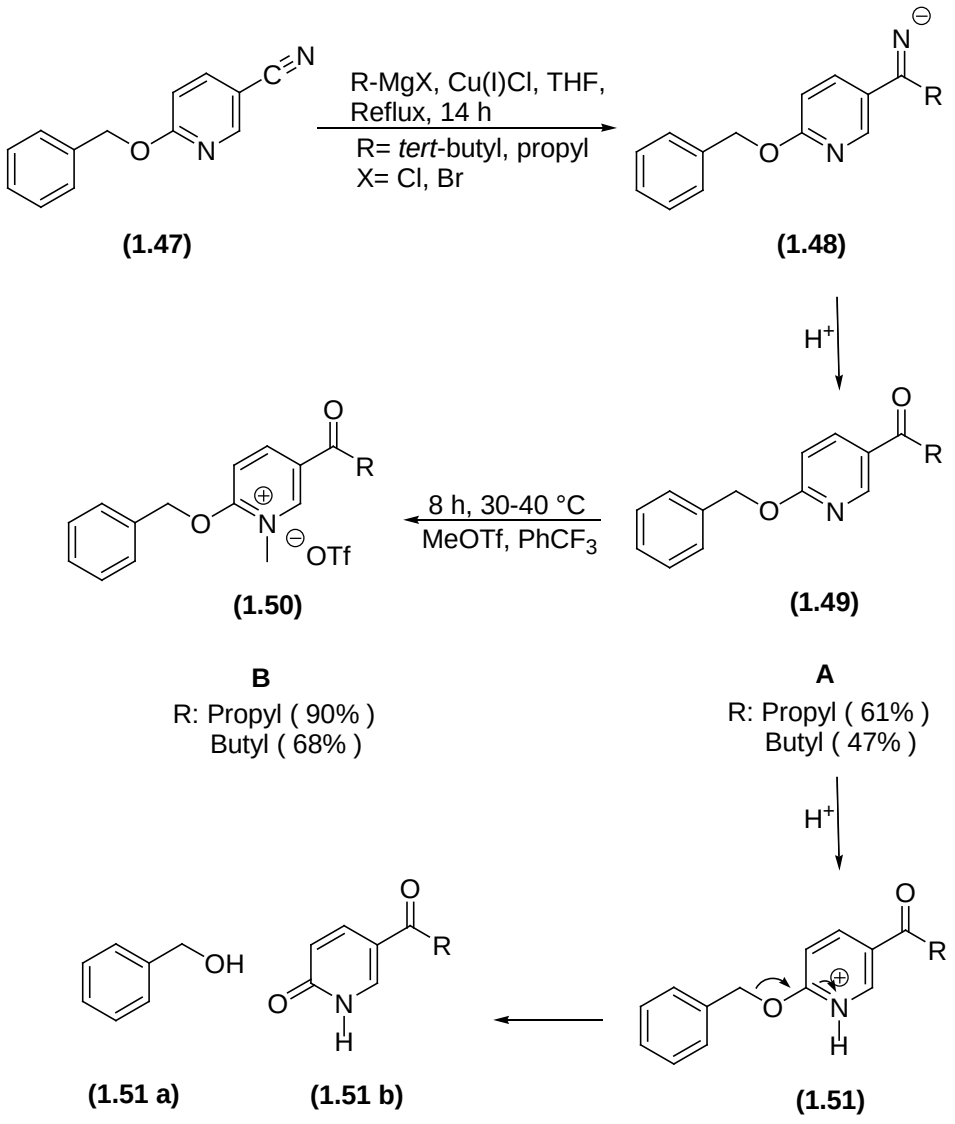


1.8 Acyl Pyridyl Derivatives

In the initial studies of the EWG derivatives, the weak EWG 5-chloro derivative, was found to have enhanced reactivity, but the impact was relatively small. On the other hand, the strong EWG derivatives were too reactive, and decomposition was occurring upon methylation. To obtain a reactivity greater than the weak EWG derivative but not to the extent of the strong EWG derivatives, a set of moderate EWG's in the form of acylpyridines, butanoyl and pivaloyl, were created to provide this moderate level of reactivity, Scheme 1.14. The synthesis of these derivatives started with 5-cyano-2-benzyloxy pyridine (**1.47**), so a Grignard addition followed by hydrolysis could generate a ketone functional group. Copper (I) chloride catalyst was used to initiate the addition, and the mixture was heated at reflux for 14h for both derivatives.[32] The reactions were quenched using a dilute acid source

to hydrolyze the anion intermediate (**1.48**) and form the precursor ether (**1.49**). Pronation of the pyridyl nitrogen could occur resulting in salt **1.51**, which should readily decompose and may have contributed to the modest overall yields of the Grignard additions (entries 1-2). The successfully synthesized ether (**1.49**) was purified using column chromatography, and then methylated using methyl triflate to form the corresponding salt (**1.50**). Methylation occurred at a higher temperature than BnOPT to form the new salt derivatives (**1.50**), because of the decreased nucleophilicity of the pyridyl nitrogen resulting from the presence of the electron-withdrawing carbonyl, Scheme 1.14.

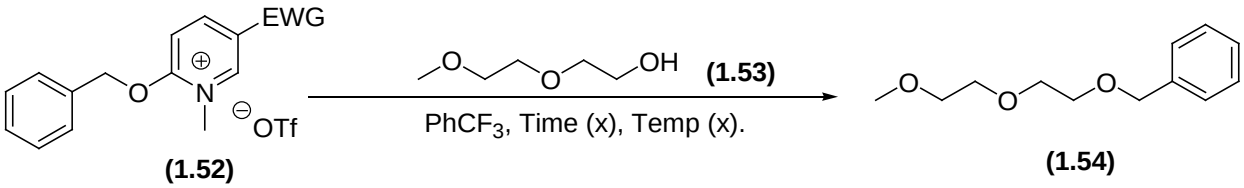
Scheme 1.14: Acyl Pyridyl Synthesis



The yields of the ketone precursors (**1.49**) varied with each R group. The pivaloyl derivative was isolated in 47% yield, but the butanoyl derivative was more consistent with yields averaging 61% (entry 1 A). The yields for the salts (**1.50**) of each precursor were more consistent for the butanoyl derivative at 90% (entry 1 B), while the pivaloyl was less efficient at 68% (entry 2 B). However, benzylation reactions using the new derivatives were significantly higher yielding and more consistent than the formation of the salts (**1.50**).

In the benzylation reactions using the two acylpyridine derivatives (**1.52**), several different temperatures (entries 2-6) were evaluated using 2-(2-methoxyethoxy)ethanol (**1.53**) as the target alcohol to determine the overall reactivity of the salts (**1.52**). Both acylpyridine derivatives were found to be reactive at lower temperatures (entries 2 and 5), and a significant decrease in reaction time was observed at 60 °C. When the reactions were stirred at 80 °C, both acylpyridine derivatives (entries 4 and 6) required 2h to reach completion, as opposed to the 24h needed for BnOPT (entry 1). Yields for the benzyl ether (**1.54**) for both of derivatives (**1.53**) at 80 °C exceeded 90% with the pivaloyl and butanoyl derivatives (**1.53**) resulting a 96 and 99% yield, respectively (entries 4 and 6), Table 1.2.

Table 1.2: Benzylation Reaction using New Derivatives



(1.52) **(1.54)**

Entry	EWG	Temperature (°C)	Time (h)	Yield (%)
1	H	80	24	93
2	Pivaloyl	40	84	94
3	Pivaloyl	60	8	93
4	Pivaloyl	80	2	96
5	Butanoyl	60	8	96
6	Butanoyl	80	2	99

The acylpyridine derivatives (entries 2-6) were found to be significantly more reactive than BnOPT (entry 1). Both the butanoyl and pivaloyl derivatives (entries 2-4) took just 2h to complete the reaction at 80 °C, while BnOPT (entry 1) took 24h to complete the reaction. The enhanced reactivity and higher yields show the derivatives (**1.53**) are more effective in the benzylation of primary alcohols than BnOPT, but there is a significant drawback in their usage.[32] The additional steps with moderate yields in their synthesis have led to higher unit cost for these derivatives which limits the overall efficiency of the derivative's usage as a benzylation reagent. To address this issue, this thesis will focus on the development of a new acylpyridine derivative and optimization of its synthesis. This new derivative should incorporate similar reactivity to the other acylpyridine derivatives but should also have enhanced solubility in aromatic solvents. The enhanced solubility will result from the additional nonpolar character of a phenyl group present within the acyl substituent, allowing for direct interaction with the nucleophile and efficient byproduct isolation for eventual recyclization of the oxypyridinium salt. These characteristics should improve the reactivity and efficiency of electrophilic transfer reactions with oxypyridinium salts.

References

1. Klein, D. R. *Organic Chemistry*. John Wiley & Sons: New York City, 2013.
2. Kocienski, P. J. *Protecting Groups: An Overview*. Thieme: Stuttgart: 2003.
3. Petri, A. F.; Bayer, A.; Maier, M. E. Total synthesis of apicularen A through transannular pyran formation. *Angew. Chem. Int. Ed.* **2004**, *43*, 5821-5823.
4. Bieg, T.; Szeja, W. Removal of *o*-benzyl protecting groups by catalytic transfer hydrogenation. *Syn. Comm.* **1985**, (1), 76-77.
5. Beyerman, H. C.; Heiszwolf, G. J. Reaction of steroidal alcohols with isobutene-usefulness of t-butyl as hydroxyl-pritecting group in a synthesis of testosterone. *J. Am. Chem. Soc* **1963**, 755.
6. Williamson, A. Theory of Aetherfication. *Philosophical Magazine* **1850**, *37*, 350-356.
7. Iversen, T.; Bundle, D. R. Benzyl trichloroacetimidate, a versatile reagent for acid-catalyzed benzylation of hydroxy-groups. *J. Chem. Soc. Chem. Commun.* **1981**, *23*, 1240-1241.
8. Hoffman, R. *Organic Chemsitry: an Intermediate Text*. 2nd ed.; John Wiley & Sons: New York City, 2004.
9. Tummarton, J.; Albiniak, P. A.; Dudley, G. B. Synthesis of benzyl esters using 2-benzyloxy-1-methyl pyridinium triflate. *J. Org. Chem.* **2007**, *72* (23), 8962-8964.
10. Poon, K. W. C. A., P. A.; Dudley, G. B. Protection of alcohols using 2-benzyloxy-1-methyl pyridinium trifluoromethanesulfonate: methyl (R)-(-)-3-benzyloxy-2-methyl propanoate. *Org. Synth* **2007**, *84*, 295.
11. Poon, K. W. C.; Dudley, G. B. Heat-and-mix benzylation of alcohols using a bench-stable pyrindium salt. *J. Org. Chem.* **2006**, *71*, 3923-3927.
12. Poon, K. W. C.; House, S. E.; Dudley, G. B. A bench-stable organic salt for the benzylation of alcohols. *Synlett*. **2005**, *20*, 3142-3144.
13. Kubota, K.; Yamamoto, E.; Ito, H. Correction to "copper(I)-catalyzed borylative exo-cyclization of alkenyl halides containing unactivated double bond". *J. Am. Chem. Soc*. **2015**, *137*, 420-424.
14. Lo Re, D.; Franco, F.; Sanchez-Cantalejo, F.; Tamayo, J. A. Total synthesis of 3-o-benzyl-1,3,5-tri-epi-calystegine B-2 from L-Sorbose. *Eur. J. Org. Chem.* **2009**, 1984-1993.
15. Longo, C. M.; Wei, L.; Roberts, M. F. Asymmetric syntheses of l,l- and l,d-di-myo-inositol-1,1'-phosphate and their behavior as stabilizers of enzyme activity at extreme temperatures. *Angew Chem Int Edit.* **2009**, *48* (23), 4158-4161.
16. Stecko, S.; Solecka, J.; Chimielewski, M. Synthesis of casuarine-realted derivatives via 1,3-diploar cycloaddition between a cyclic nitrone and an unsaturated gamma-lactone. *Carbohydrate Res.* **2009**, *344*, 167-176.
17. Taber, D. F.; Nelson, C. G. Aliphatic C-H to C-C conversion: Synthesis of (-)-cameroonan-7 alpha-ol. *J. Am. Chem. Soc*. **2011**, *76*, 1874-1882.
18. Trotter, T. N.; Albury, A. M. M.; Jennings, V. K. Total synthesis of 7-deoxy-6-O-methylfuraserntin featuring a chelation-controlled 1,3-reetz keck-type allylation. *J. Org. Chem.* **2012**, *77*, 7688-7692.
19. Fulo, H. F.; Albiniak, P. A.; Dudley, G. B. Protection of alcohols using 2-benzyloxy-1-methylpyridinium trifluoromethanesulfonate: Methyl (R)-(-)-2-methyl propanoate. *Org. Synth*. **2019**, *96*, 124-136.
20. Lam, H.; House. S. E.; Dudley, G. B. The para-siletanylbenzyl (PSB) ether: a peroxide-cleavable protecting group for alcohols and phenols. *Tetrahedron Lett.* **2005**, *46* (19), 3283-3285.
21. Culy, C. Exploring the reactivity of oxypyridinium salt derivatives with oxygen nucleophiles. Ball State University, 2016.
22. Salvati, A.; House, C.; Albiniak, P. A. Acid and isobutylene-free synthesis of t-butyl ethers by in situ formation of 2-t-butoxy-1-methylpyridinium triflate. *Tetrahedron Lett.* **2014**, *55* (51), 7133-7135.
23. Greene, T. W., Wuts, P. G. M. *Protecting Groups in Organic Synthesis*, 4th Ed.; John Wiley and Sons: New York, **2007**.

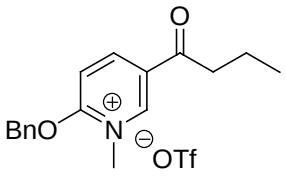
24. Albiniak, P. A.; Dudley, G. B. Thermally generated phenyl carbenium ions: acid-free and self quenching Friedel-Crafts reactions. *Tetrahedron Lett.* **2007**, *48* (46), 8097-8100.
25. Friedel, C.; Crafts, J. M. Sur une nouvelle methode generale de synthese d'hydrocarbures, d'acetones, etc. *Compt. Rend.* **1877**, *84*, 1392.
26. Strayer, T.; Culy, C.; Frank, A.; Albinaik, P. In situ synthesis of 2-allyloxy-1-methylpyiridinium triflate for the allylation of carboxylic acids. *Tetrahedron Lett.* **2015**, *56*, 6807-6809.
27. Jeffery, P. D.; McCombie, S. W. Homogenous, palladium (0)-catalyzed exchange deprotection of allylic esters, carbonates, and carbamates. *J. Org. Chem.* **1982**, *47*, 587-590.
28. Zhang, H. X.; Guibe, F.; Balavoine, G. Selective paladium-catalyzed deprotection of the allyl and allyloxycarbonyl groups in phosphate chemistry in the presence of propargyl and propargyloxycarbonyl groups. *Tetrahedron Lett.* **1988**, *29* (6), 623-626.
29. Plante, O.; Buchwald, S.; Seeberger, P. Halobenzyl ethers as protecting groups for organic synthesis. *J. Am. Chem. Soc*. **2000**, *122*, 7148-7149.
30. Nwoye, E. O.; Dudley, G. B. Synthesis of para-methoxybenzyl (PMB) ethers under neutral conditions. *Chem. Comm.* **2007**, 1436-1437.
31. Bakshi, T. Substituents effects on the synthesis and reactivity of 2-benzyloxypyridinium trifalte derivatives. M.S. Thesis, Ball State University, 2014.
32. Harry, S., Unpublished work from the Albiniak lab. 2016.

Chapter 2
Byproduct Isolation and Benzoyl Derivative Development

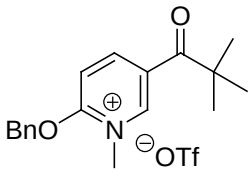
2.1 Introduction

In the initial studies of electron withdrawing group (EWG) oxypyridinium salt derivatives as discussed in Chapter 1, weak and strong EWG derivatives were found to have significant reactivity at lower temperatures. However, the optimal level of reactivity was not achieved with these derivatives, as seen with the weak EWG derivative having only slightly greater reactivity than BnOPT, Table 1.1 (entry 2). The efficiency in using the strong EWG derivatives was poor, because of the higher temperature required for methylation would result in the salt's decomposition upon its formation, Table 1.1 (entries 4-6). The longer time required for methylation and the reduced nucleophilicity of the pyridyl nitrogen atom of the strong EWG precursors could also lead to competitive methylation of the alcohol, resulting in an overall lower yield of the desired benzyl ether, Table 1.1 (entries 4-6). A balance between the conditions required to synthesize and decompose the EWG derivatives was required to optimize benzyl transfer. A pair of moderate EWG acyl derivatives, butanoyl (**2.1**) and pivaloyl (**2.2**), were developed to provide the balance between formation and reactivity, Figure 2.1.

Figure 2.1: Ketone Derivatives



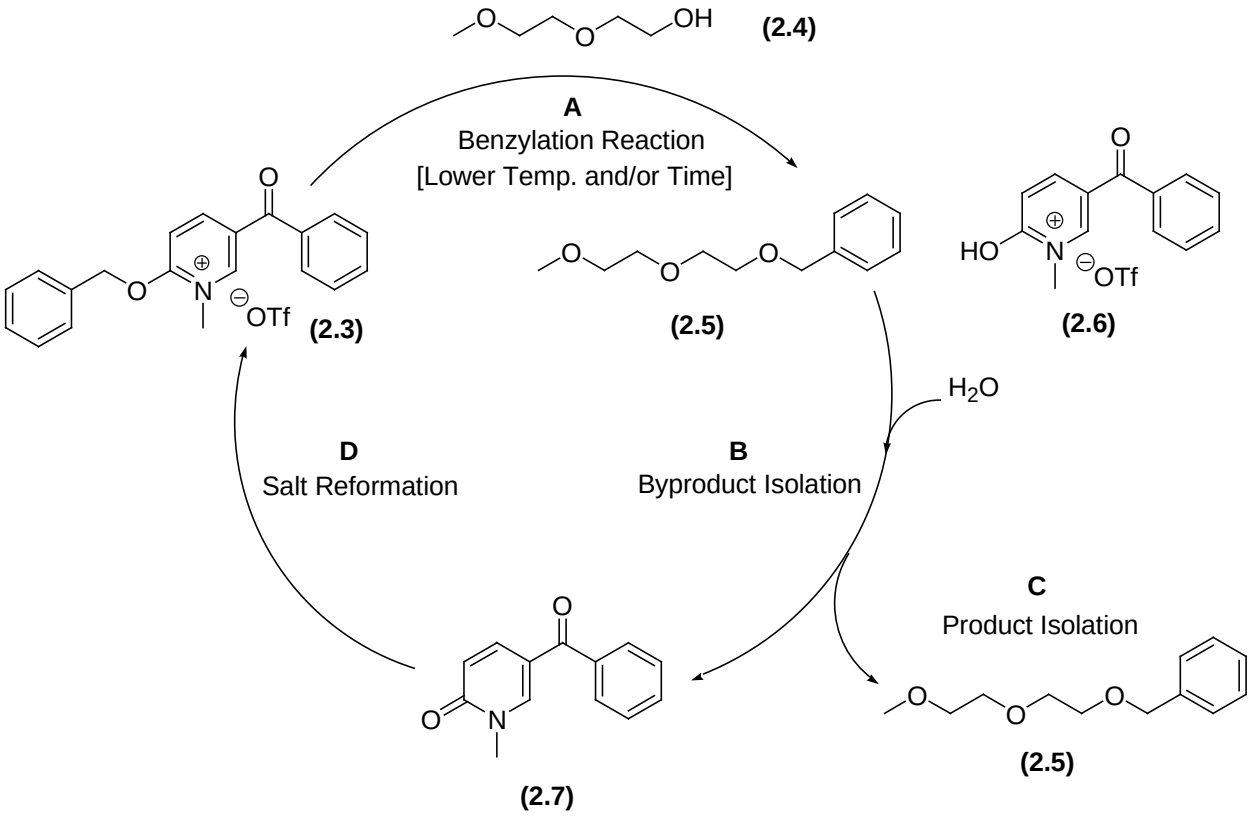
(2.1)



(2.2)

These acyl-substituted derivatives (**2.1** and **2.2**) were found to be significantly more reactive than the weak EWG derivative, but not to the extent of decomposing directly upon methylation like the strong EWG derivatives. This moderate level of reactivity makes the usage of these new salts (**2.1** and **2.2**) advantageous over the other EWG salts because of their enhanced reactivity and ability to be stored for later usage. A drawback to the usage of these derivatives (**2.1** and **2.2**) is their higher, expected unit cost, due to the additional steps required in their synthesis. This project will focus on addressing this problem through the development and optimization of the synthesis of a new benzoyl substituted oxypyridinium salt (**2.3**). The isolation of its byproduct (**2.6**) following a benzylation of an alcohol will be investigated as a means of increasing the cost efficiency of these reagents. The salt (**2.3**) can potentially be recycled from the byproduct (**2.6**) to increase its (**2.3**) overall efficiency as a benzylation reagent, Figure 2.2.

Figure 2.2: Proposed Benzoyl Derivative and its Recyclization

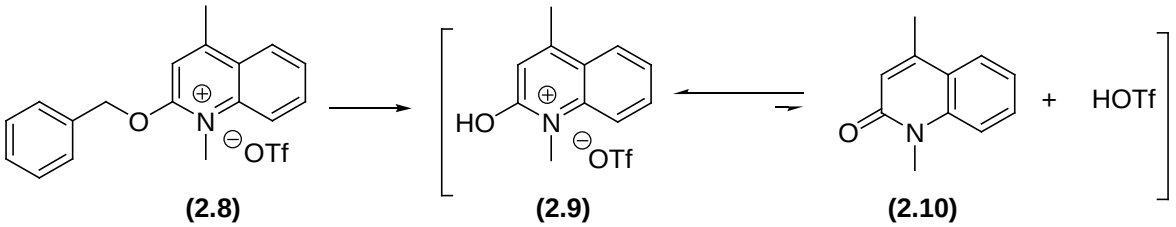


2.3 is also expected to possess enhanced solubility which will provide several advantages over the other derivatives (**2.1** and **2.2**). One of the advantages is greater reactivity, because of better interaction between **2.3** and the alcohol (**2.4**). Another advantage is the byproduct (**2.7**) isolation is expected to be more efficient, due to the previously mentioned non-polar character of the phenyl ring allowing for greater solubility in aromatic solvents and decreasing solubility in water. In order to determine an ideal method for byproduct (**2.7**) isolation, a set of preliminary experiments using decomposed salt samples of lepidine and butanoyl (**2.1**) variants were performed.

2.2 Salt Byproduct Recovery Isolation Studies

An older decayed sample of a BnOPT derivative, 2-benzyloxy-1-methyllepidinium triflate (BnOLT) (**2.8**), was used initially to determine a method of isolating salt byproduct. This sample was chosen because it was composed of lepidine salt (**2.8**) and 2-hydroxy-1-methyllepidinium triflate (**2.9**). Separation of the two compounds (**2.8** and **2.9**) was first attempted using recrystallizations. Solvents were chosen to cover a range of polarities from very polar solvents, such as water, to relatively nonpolar solvents, such as $PhCF_3$. The solvent used in each recrystallization attempt was added to 5 mL test tubes, where a small amount (12-15 mg) of the decomposed lepidine sample was heated to 60 °C using a water bath. Once the solid had been completely dissolved, the tubes were removed from the bath and cooled to room temperature. Initial precipitation was only observed in the ethyl acetate trial (entry 3) in form of cloudiness at the top of the solution, but a definitive, isolable solid was not formed. The tubes were then cooled 0 °C overnight to induce crystallization. In trail 1, hexanes were added to see if the byproduct (**2.9** and **2.10**) could be extracted in the formed organic layer; however, precipitant was found to have only formed in the aqueous layer at the bottom of the test tube, Table 2.1.

Table 2.1: Initial Solvent Screening of Decomposed Lepidine Sample



(2.8) **(2.9)** **(2.10)**

Initial				Final		
Entry	Solvent	Source Ratio (**2.8**/**2.9**)	Initial (mg)	Final Composition	Final (mg)	Tautomer Recovery(%)
1	Water	0.09 / 0.91	12.9	**2.10 (only)**	5.9	46
2	Ethanol	0.09 / 0.91	14.2	-	-	-
3	Ethyl Acetate	0.09 / 0.91	12.4	**2.9 (only)**	1.5	12
4	Chloroform	0.09 / 0.91	15.9	-	-	-
5	Trifluorotoluene	0.09 / 0.91	14.5	-	-	-

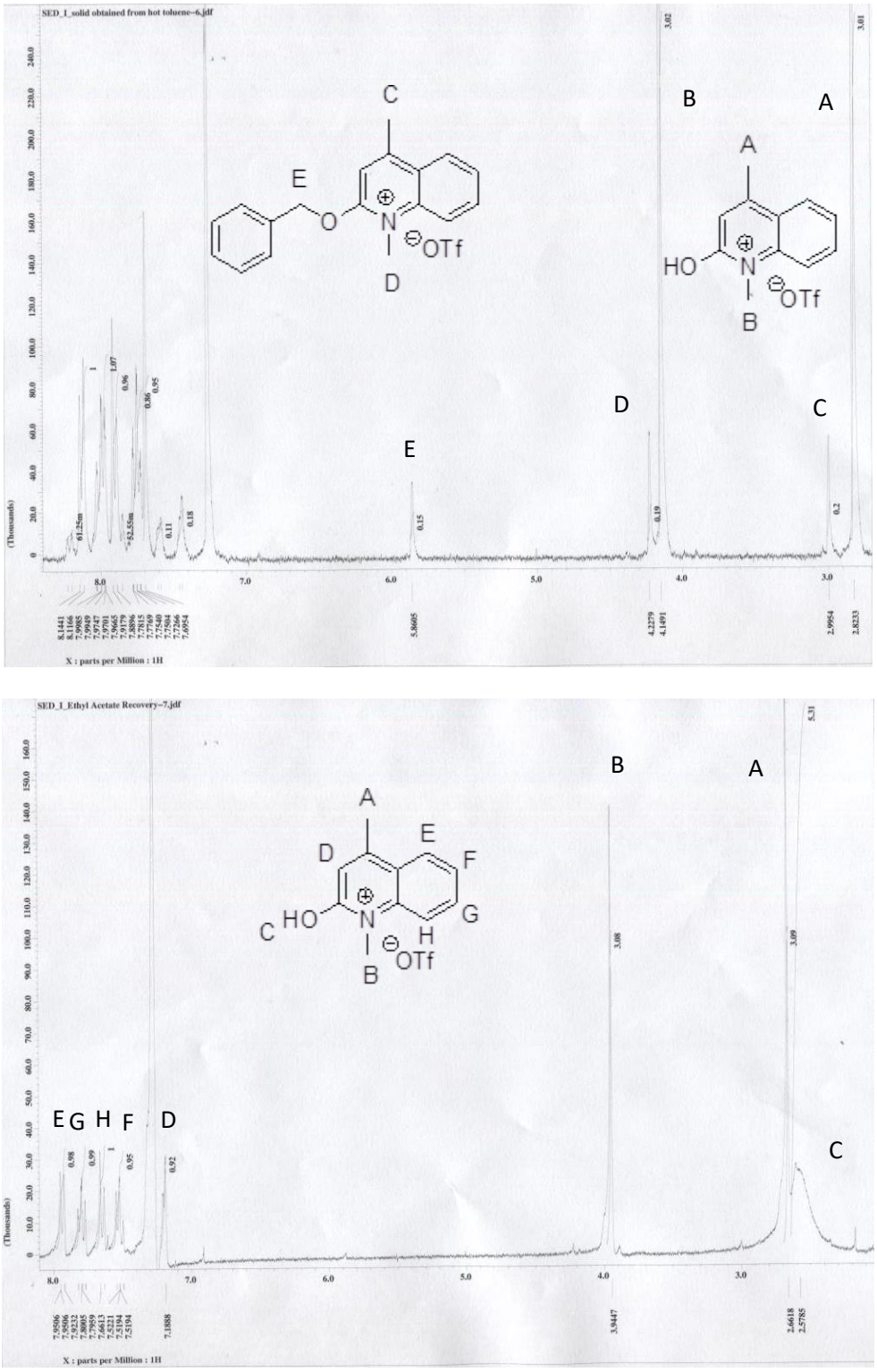
[a.] Source ratio determined by a comparison between the integration of ^{1}H NMR peaks A (**2.9**) and C (**2.8**) (Ratio = $\frac{A}{C}$).

[b.] 2-hydroxylepidine (**2.8**) was the only tautomer observed in the source spectra.

[c.] The final composition refers to the tautomer observed by ^{1}H NMR in the precipitant.

Recoveries varied with each trial, which may have resulted from the low masses of sample used in comparison to the larger volume of solvent used. Of the solvents analyzed, EtOAc (entry 3) was found to successfully isolate **2.9**, while the recrystallization using water (entry 1) did yield a precipitant of **2.10**. The lepidone (**2.10**) resulted from the deprotonation of **2.9** by water and removal of the triflate counter anion as $H_3O^+OTf^-$, Figure 2.3.

Figure 2.3: Sample Source Spectra (Top), 2-Hydroxy Lepidine Spectra (Bottom)

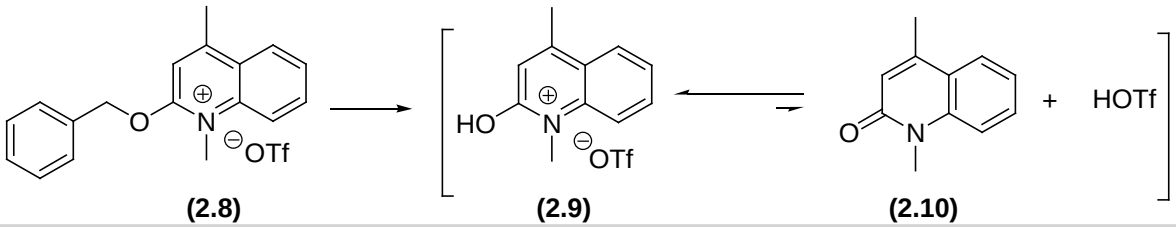


[a.] Both spectra, Figure 2.3, were taken using a 300 MHz NMR.

The other solvents used (entries 2, 4-5) did not result in any recrystallization, even after refrigeration overnight, so further recrystallization studies did not include solvents. The next set of recrystallizations was focused initially on mixtures of EtOAc and hexanes to determine an ideal polarity for isolating **2.8**.

For the EtOAc recrystallizations, decomposed salt sample mixtures were placed in test tubes, and a specific volume of EtOAc was added to each of the tubes. In one trial (entry 1), 1 mL of hexanes was added to make the solution more nonpolar prior to heating. After the solid dissolved with heating in the solution for each of the trials, the solution was cooled to room temperature and precipitation was not observed. 1 mL of hexanes were added to each tube and a cloudy composition was observed, and the solutions were then cooled to 0 °C and left overnight to induce complete crystallization. Source and product ratios were determined by comparing integrations of peaks A and C shown in Figure 2.3 (Top). Both the initial and final masses were determined by multiplying the measured mass by either source or product ratio, Table 2.2.

Table 2.2: Ethyl Acetate Recrystallizations



(2.8) **(2.9)** **(2.10)**

	Initial					Final		
	EtOAc	Hexanes initial	Hexanes final	Source Ratio[a]	Initial[b]	Product Ratio[a]	Final[b]	Recovery
Entry	(mL)	(mL)	(mL)	(**2.8**/**2.9**)	**2.9** (mg)	(**2.8**)/(**2.9**) or (**2.10**)	**2.9** or **2.10** (mg)	(%)
1	6	1	1	0.83 /0.17	40.8	0.89 (**2.8**)/ 0.11 (**2.10**)	4.0	10
2	4	0	1	0.83 /0.17	15.2	0.6 (**2.8**)/ 0.4 (**2.9**)	3.9	26
3	9	0	1	0.83 /0.17	33.8	0.75 (**2.8**)/ 0.25 (**2.10**)	13.6	40

[a.] Both Source and Product Ratios were determined by a comparison between the integration of peaks A and C (Ratio = $\frac{A}{C}$) observed in Figure 2.3.

[b.] Both Initial and Final masses were determined by multiplying the measured mass of either the initial or final mixture by the estimated composition; ex. (Final mass= (Product Ratio)(Final (mg)).

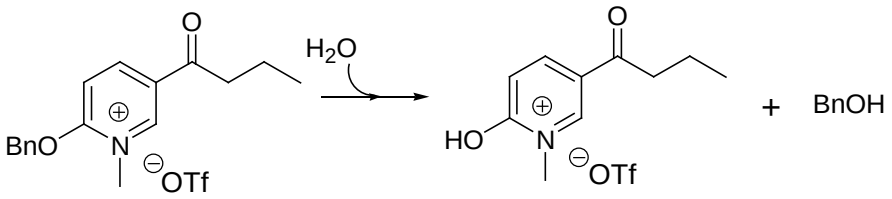
The results were inconsistent in comparison the original EtOAc recrystallization, Table 1.1, entry 3, as combinations of either **2.9** or **2.10** with **2.8** were produced (entries 1-3) in each of the trials.

Recoveries were low in all the trials, which may have been attributed to the larger volume of solvent used in comparison to the sample source's mass (entries 1-3). Given the tubes containing the sample were open to atmospheric air during the heating, **2.9** may have been deprotonated by absorbed water to form **2.10**, entries 1 and 3. Given the inconsistencies of the recrystallizations, another possible method for byproduct isolation, trituration, was investigated using a completely decomposed sample of butanoyl salt (**2.1**).

2.3 Isolation of Butanoyl Byproduct

A sample of completely decayed **2.1** was used in a solvent screen to determine if isolating the byproduct by trituration was possible. **2.1** was assessed due to its similar chemical structure to the benzoyl derivative (**2.3**). All triturations were performed in test tubes where the solid was suspended in 2 mL of diethyl ether and stirred for 10 seconds to induce separation. Undissolved solid (**2.11**) was isolated from the solvent by vacuum filtration and evaluated with ^{1}H NMR to determine if the byproduct (**2.11**) was present.

Table 2.3 Butanoyl Byproduct Trituration



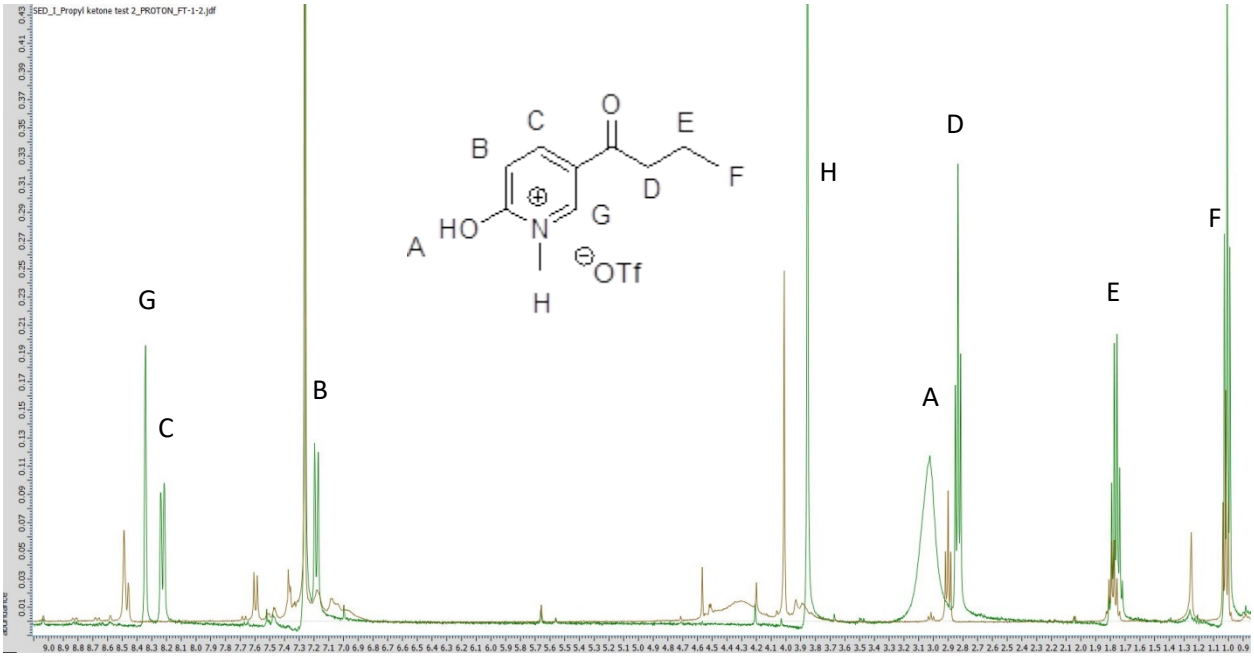
(2.1) **(2.11)** 72-75%

Initial			Final	
Entry	Solvent	Crude **2.11** (mg)	Pure **2.11** (mg)	Recovery (%)
1	Ethyl Acetate	23.1	-	-
2	Acetonitrile	19.9	-	-
3	Dichloromethane	19.3	-	-
4	Chloroform	21.1	-	-
5	Diethyl Ether	19.2	15.0	78
6	Diethyl Ether	42.9	33.8	79
7	Diethyl Ether	87.3	66.0	76

[a.] Initial mass of (**2.11**) determined from estimated % composition using the source ^{1}H NMR ((% composition) x (initial sample mass) = initial mass byproduct).

Most solvents (entries 1-4) completely dissolved the sample and did not leave behind a solid residue, but diethyl ether (entry 5) did leave behind a brown crystalline powder that was identified as **2.11** by ^{1}H NMR. This trituration was repeated twice (entries 6-7) to confirm the original findings. Each trial using diethyl ether showed evidence of **2.11** in ^{1}H NMR spectra, and the recoveries varied between 72-75%, Table 2.5. The recovery is based on the mmols of **2.11** obtained after the trituration in comparison to the mmols present in the original sample. The difference of purity between sample source and isolated **2.11** can be seen in the sample source ^{1}H NMR spectra compared to a ^{1} H NMR spectrum of a sample obtained from trituration, Figure 2.4.

Figure 2.4: Source Sample (Brown) and Sample after Diethyl Ether Trituration (Green)



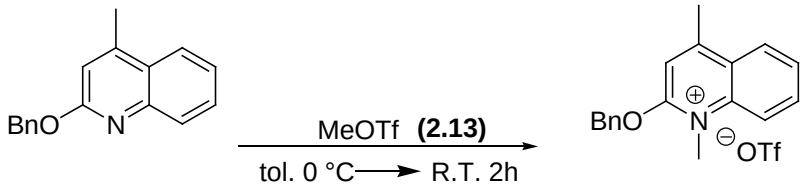
Peaks attributed to **2.10** are seen in the sample source spectra, but there are also peaks associated with benzyl alcohol seen at 3.833-4.567 and 6.997-7.354 ppm in the sample source at the aromatic region, Figure 2.4 (**Brown**). After the diethyl ether trituration, both regions are significantly cleaner leaving only peaks associated with the **2.10**. These triturations provided insight on the possible insoluble character of the ketone derivatives (**2.1-2.3**) in diethyl ether, and the application of this trituration following a transfer reaction could provide a simple method of separating the benzyl ether from benzoyl byproduct (**2.7**). To test this method of byproduct isolation in an actual reaction mixture of salt and alcohol, lepidine (**2.8**) was used in a pair of transfer reactions with the goal of successfully separating and isolating the byproduct from the produced benzyl ether.

2.4 Byproduct Recovery from Transfer Recovery

To determine the feasibility of byproduct recovery following a transfer reaction, a sample of pure **2.8** was synthesized from 2-benzyloxylepidine (**2.12**) by alkylating with methyl triflate (**2.13**). The

synthesis followed a similar procedure outlined for the synthesis of PMB lepidine derivative,[1] Scheme 2.1, and resulted in smooth conversion to the triflate salt (**2.8**).

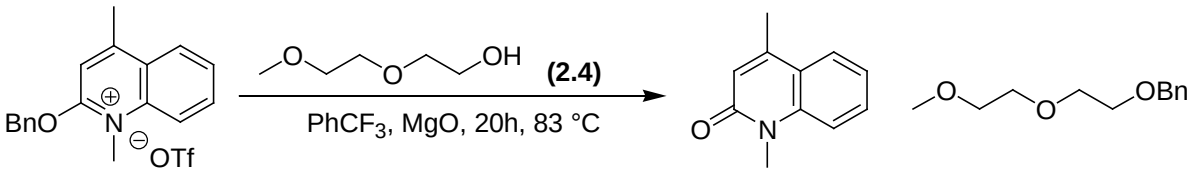
Scheme 2.1 Synthesis of 2-Benzyloxy-1-Methyllepidinium Triflate



(2.12) **(2.8)** 83%

An 83% yield was obtained for **2.8**, and it was reacted in two separate transfer reactions with 2-(2-methoxyethoxyethanol (**2.4**), with a focus on the recovery of **2.10**, Table 2.5. Both crude reaction mixtures were subjected to column chromatography, and the first transfer reaction resulted in a successful isolation of **2.10** using an eluent of 99:1 DCM:ethanol with a 91% yield (entry 1). The second transfer reaction did not lead to a successful separation of the byproduct, because the initial eluent was too polar. This eluent resulted in both the benzyl ether (**2.5**) and **2.10** passing through the silica gel stationary phase simultaneously without efficient separation. The resulting impure sample was then triturated twice with diethyl ether, resulting in significant separation of **2.10** from **2.5**. The remaining portion was obtained using column chromatography with the 99:1 DCM:ethanol eluent used in the previous trial to obtain an overall 74% yield of byproduct (entry 2). Some of the **2.10** lepidone was dissolving in the diethyl ether during this trituration; therefore, this method of isolation is not necessarily optimal for the general separation of the byproduct for all oxypyridinium salts, Table 2.4.

Table 2.4: Lepidone Recovery after a Transfer Reaction



(2.8) **(2.10)** **(2.5)**

Entry	BnOLT (g)	Lepidone (g)	Byproduct yield (%)	Method
1	0.5586	0.2132	91	Column (Only)
2	0.4158	0.1283	74	Column and Diethyl Ether Trituration

[a.] The byproduct yields were calculated based on the equimolar ratio between the salt used and the byproduct isolated.

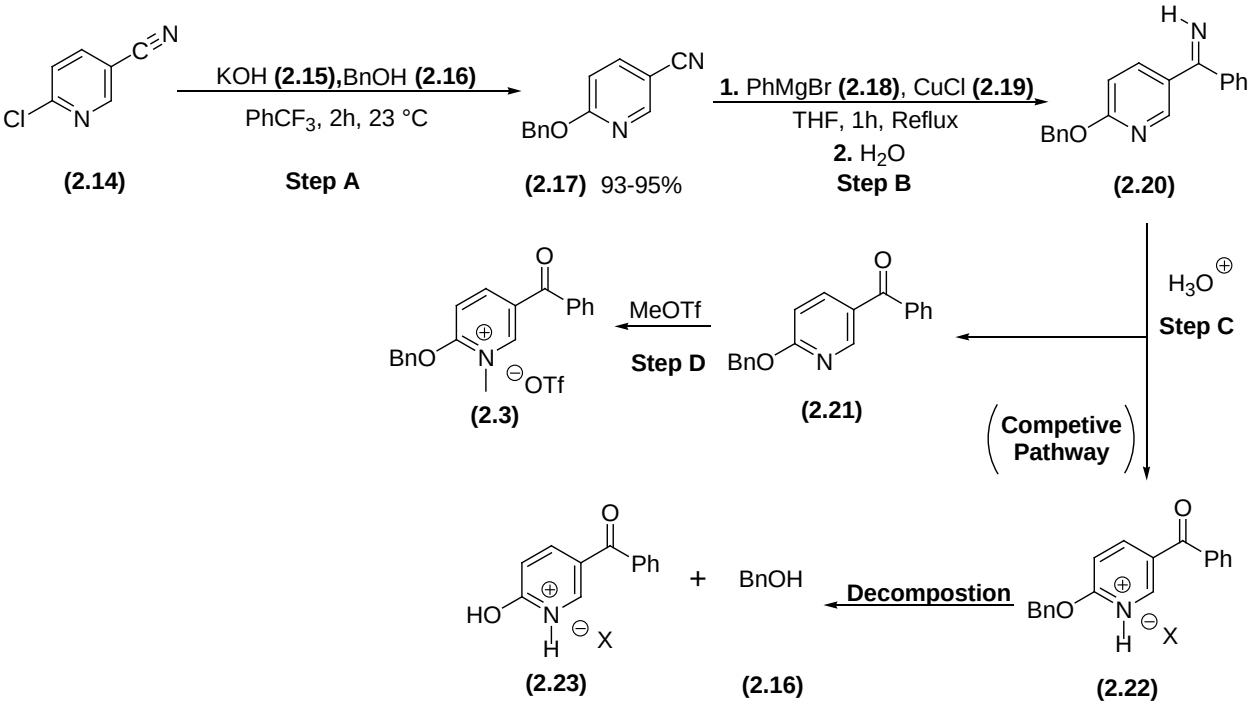
These experiments do show proof of principle that the pyridone/lepidone byproduct of oxypyridinium salt transfer reactions can be separated and recovered. With both the lepidinium (**2.7**) and butanoyl (**2.1**) derivatives evaluated, and the success of the diethyl ether trituration isolating the butanoyl byproduct (**2.10**), development of the newly proposed benzoyl derivative (**2.3**) was undertaken.

2.5 Benzoyl Salt Derivative Synthesis

The proposed synthesis of the benzoyl derivative (**2.3**) is very similar to the previous syntheses of the butanoyl (**2.1**) and pivaloyl (**2.2**) salts, because of the shared steps including a Grignard addition and methylation, Table 1.2 in Chapter 1. The initial step of **2.3**'s total synthesis is the formation of 2-benzyloxy-5-cyanopyridine (**2.13**). The reaction consists of stirring 2-chloro-5-cyanopyridine (**2.14**) with benzyl alcohol (**2.16**) in the presence of a base, KOH (**2.15**), over a 2h period at 23 °C (Step A), and the resulting solid was recrystallized using hexanes to obtain a yield of 93-95%. This reaction is a very similar to the synthesis of 2-benzyloxypyridine, but the reaction occurs readily at room temperature due to the nitrile and pyridine nitrogen stabilizing the ring for a S_NAr reaction to occur more efficiently. The resultant 5-cyano ether (**2.17**) was reacted with phenyl Grignard reagent (**2.18**) at reflux in THF for 1h with Cu(I)Cl catalyst (**2.19**).[2] The Grignard addition of the phenyl group (Step B) is more feasible than the t-butyl or propyl Grignard additions, due to the phenyl ring having a concentrated electron density resulting from its sp^2 orbitals as opposed to the propyl and t-butyl groups sp^3 orbitals. The phenyl ring also possesses less steric hinderance than t-butyl groups, due to the predicted flat structure of the ring. An imine (**2.20**) is produced from the addition by quenching with water (Step B) and the hydrolysis of **2.20** into the corresponding ketone (**2.21**). However, if the reaction mixture becomes too acidic,

protonation of the pyridyl nitrogen of the benzoyl ether (**2.22**) can occur and result in the decomposition of **2.22** into a 2-hydroxypyridinium byproduct (**2.23**) and benzyl alcohol (**2.16**), Scheme 2.2 (Step C). To avoid this undesired protonation, different acids and concentrations will be assessed to determine the most ideal conditions for hydrolysis of imine **2.20**.

Scheme 2.2: Proposed Pathway and Competitive Pathway in Benzoyl Derivative Synthesis

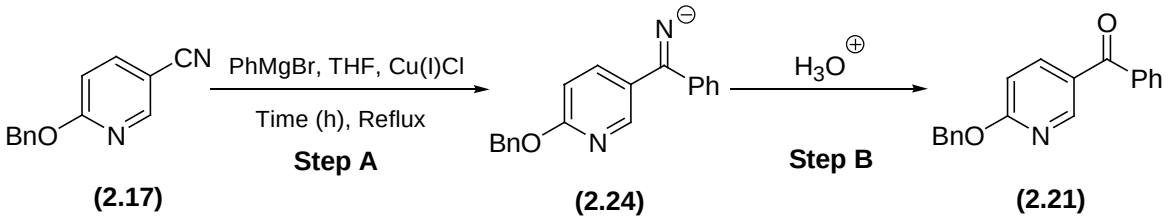


2.21 produced from the hydrolysis will be purified and methylated to yield **2.3**. The methylation is expected to occur under slightly milder conditions than the butanoyl (**2.1**) and pivaloyl (**2.2**) derivatives, Figure 2.5 (Step D), due to the phenyl ring reducing the electron-withdrawing capability of the acyl group relative to the alkyl derivatives **2.1** and **2.2**, Scheme 2.2. Prior to the formation of the salt, the ideal conditions for the phenyl Grignard addition were assessed to produce ketone **2.21.**

2.5.2 Phenyl Grignard Addition

An investigation into the necessary conditions for the Grignard addition (**Step A**) and subsequent hydrolysis (**Step B**) were conducted in a step-wise manner, and the first set of experiments focused findings the ideal conditions of the Grignard addition, Figure 2.5.

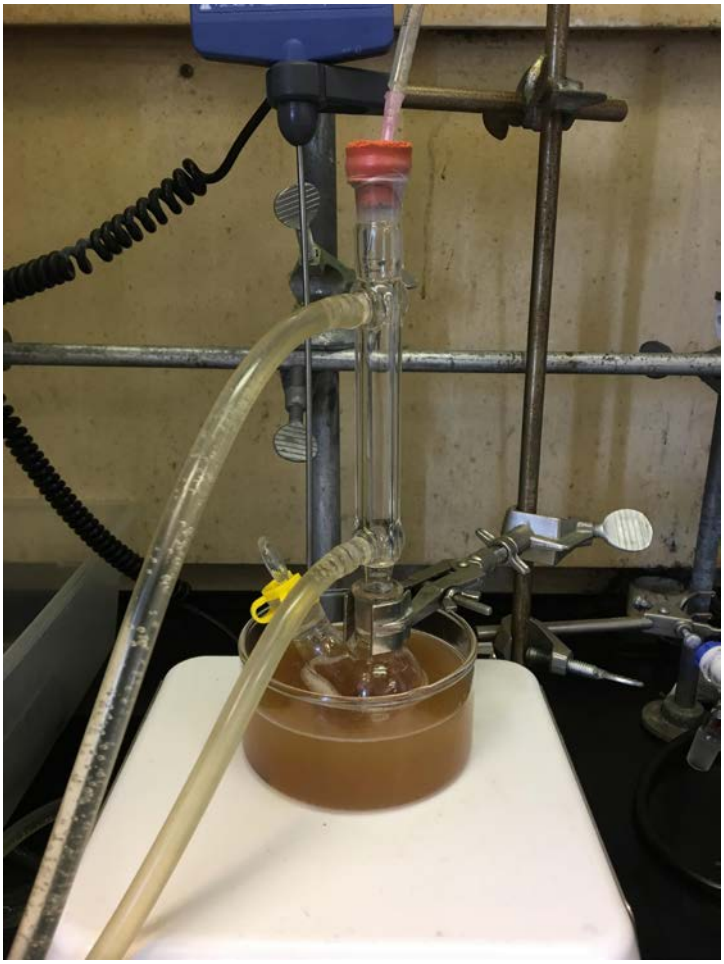
Figure 2.5: **Stepwise Grignard Addition and Hydrolysis**



(2.17) **(2.24)** **(2.21)**

An *in situ* Grignard formation and addition were used to generate the precursor molecule (**2.21**) for the new salt (**2.3**), and a specific setup was needed to maintain anhydrous conditions while the reaction occurred, Figure 2.6.

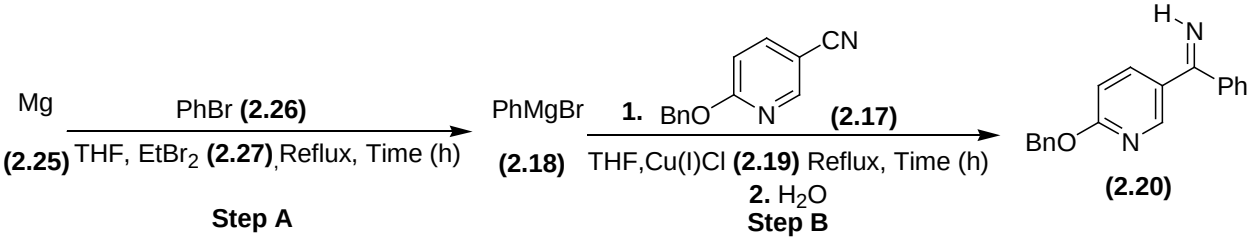
Figure 2.6: Anhydrous Setup for *In Situ* Grignard Formation and Addition



In the first step of the *in situ* reaction, magnesium shavings (**2.25**) were weighed in a two neck round bottom flask shown in Figure 2.6. The system was placed under vacuum once a glass stopper and reflux condenser were attached, and the glassware was then flame dried and placed under argon prior to adding THF and dibromoethane (**2.27**). The 1,2-dibromoethane (**2.26**) serves to expose the magnesium's surface to bromobenzene (**2.26**) for the formation of the Grignard reagent (**2.18**).[3] A slight excess of bromobenzene (**2.26**), previously diluted with THF, would be added by syringe at 0 °C over 10 min. The solution would then be allowed to stir at reflux for 1.5h to form the Grignard reagent (**2.18**), and a

similar technique would be used for the addition of the nitrile (**2.17**) to the formed Grignard reagent (**2.18**). Cu(I)Cl (**2.19**) was added to the solution upon the complete addition of the nitrile (**2.17**) to catalyze the Grignard addition (Step B), Table 2.5.[3]

Table 2.5 Varying Conditions of Grignard Reactions



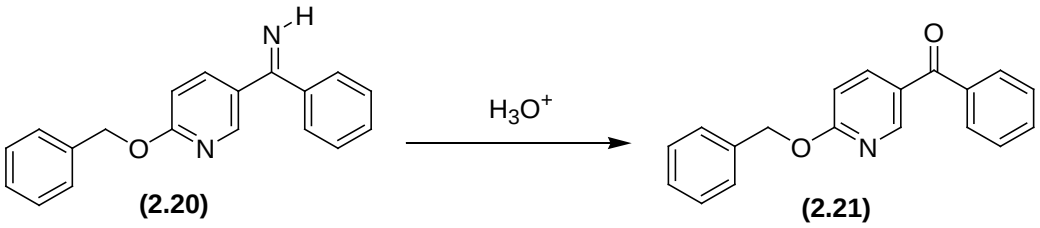
	Step A		Step B	
Entry	Additives	Grignard formation (h)	Time (h)	Conversion (Imine/Nitrile)
1	None	1.5	14	66/33
2	Cu(I)Cl	1.5	2.5	75/25
3	$EtBr_2$+Cu(I)Cl	0.5	3	33/66
4	$EtBr_2$+Cu(I)Cl	1	3	95/5
5	$EtBr_2$+Cu(I)Cl	1.5	3	$\geq$99/1
6	$EtBr_2$+Cu(I)Cl	1.5	2	$\geq$99/1
7	$EtBr_2$+Cu(I)Cl	1.5	1	$\geq$99/1

The usage of dibromoethane (**2.27**) was found to be essential for a complete formation of the Grignard reagent (**2.18**) (entries 1-2). The time at reflux for the Grignard formation and addition were also crucial for the synthesis of imine (**2.20**) to reach completion, Table 2.5. For the formation of the Grignard reagent (**2.18**), any time less than an hour (entries 3-4) resulted in an incomplete formation, and an ideal time (entry 5-7) for the formation of the Grignard reagent (**2.18**) was determined to be a 1.5h at reflux. A brown colored solution was produced after 1.5h providing a physical indicator of the reagent's (**2.18**) formation.

The optimal time at reflux for the Grignard addition was found to be 1h (entry 7) resulting in complete consumption of the imine starting material. Based on these set of experiments, a partially

optimized procedure determined for the Grignard formation and addition consist of a 1.5h reflux for the formation of the reagent (**2.18**) and 1h reflux for the addition (entry 7). The solution was quenched with water to produce the imine (**2.20**). An obstacle in hydrolysis of the imine is the possible competitive protonation of the pyridyl nitrogen as opposed to the desired protonation of the imine. This undesired protonation could cause the resultant salt (**2.21**) to decompose into the corresponding cation/anion pair. To determine an appropriate acid source which would cause hydrolysis with minimal protonation of the pyridyl nitrogen and subsequent decomposition, a screening of different protic acids used to hydrolyze the imine (**2.19**) was performed, Table 2.6.

Table 2.6: Varying Solutions for Conversion of Imine to Ketone



(2.20) **(2.21)**

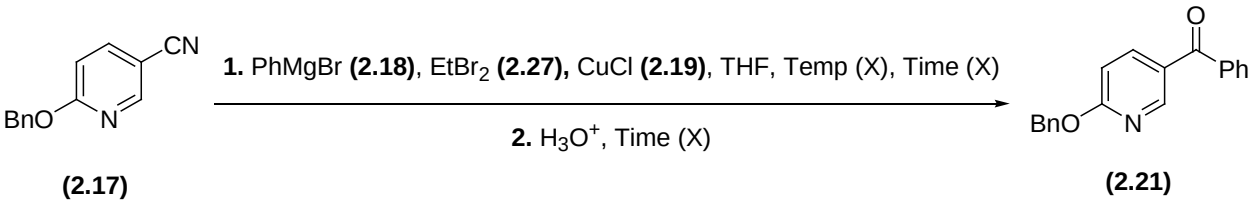
Entry	Acid	pH	Time (h)	Conversion (Ketone:Imine)
1	satd. NH_4Cl	3.77	22	36/64
2	1% Acetic Acid	3.90	16	>1/99
3	5% Acetic Acid	3.55	12	$\geq$99/1
4	10% Acetic Acid	3.10	16	$\geq$99/1
5	1% Sulfuric Acid	1.02	10	$\geq$99/1

[a.] These experiments did not have recorded yields, because the recoveries were combined prior to purification were combined prior to purification.

The imine (**2.17**) was diluted with 2 mL of solvent for four of the trials (entries 1-5). Satd. NH_4Cl (entry 1) was unsuccessful in hydrolyzing all the imine (**2.20**) in a 24h period (entry 1), and the 1% acetic acid (entry 2) was unsuccessful in hydrolyzing any of the imine (**2.20**) after 16h. Evidence of a pH threshold becomes apparent for a timely hydrolysis as acid sources 5% acetic acid through 1% sulfuric acid (entries 3-5). This data does not provide complete confirmation as to whether decomposition was

occurring but instead shows the consumption of **2.17**. These experiments indicate complete conversion in both steps towards formation of the ketone (**2.21**), Table 2.7.

Table 2.7: One-Pot Synthesis



(2.17) **(2.21)**

Entry	PhMgBr addn. (h)	Aqueous Acid	Time (h) Hydrolysis	Yield (%)	Solution (pH)
1	3	5% Acetic Acid	16	68	3.55
2	3	10% Acetic Acid	12	51	3.10
3	2	1% Sulfuric Acid	10	71	1.02
4	2	12% Sulfuric Acid	16	26	-0.05

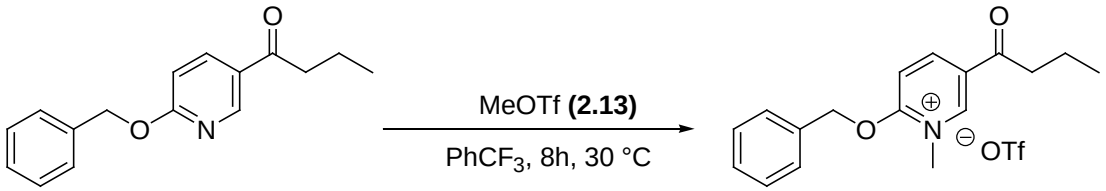
One-pot synthesis was first completed using an initial Grignard reagent (**2.18**) followed by addition of **2.17**. After a set time to allow a complete addition, the acid would be added drop wise at 0 °C, and the mixture was warmed to room temperature and stirred for an extended period of time. Purification of the one-pot reaction recovery was performed using column chromatography with a 19:1 hexanes/EtOAc eluent to obtain a clear liquid. The yield using 12% sulfuric acid (entry 4) was significantly lower than all the other trials (entries 1-3), and it may have resulted from extensive protonation of the pyridyl nitrogen and subsequent decomposition of the product (**2.21**). An anomalous behavior was observed between entries 1 and 3, because the usage of the less acidic 10% acetic solution resulted in a lower yield than 1% sulfuric acid. Based on Table 2.6, both reactions should have consumed all the starting material, but the difference in solubility between acetic acid and sulfuric acid may have been a factor in the difference of yields. In terms of solubility, acetic acid is more soluble in THF than sulfuric acid, and this higher solubility may have led to more significant protonation of the pyridyl nitrogen. To optimize the one-pot synthesis, an acetic acid solution with a pH lower than satd. NH_4Cl, pH = 3.77, (entry 1) but not to extent of 5% acetic acid, pH = 3.55, (entry 3) would be ideal, Table 2.7. A more dilute

sulfuric acid solution, such as 0.5% sulfuric acid, may be more effective than a more dilute acetic acid solution in hydrolysis, due to the limited solubility of sulfuric acid in THF. A significant amount of ether (**2.21**) was produced from these trials, and the ether (**2.21**) was used to determine the ideal conditions of methylation of the formation of the salt (**2.21**).

2.5.3 Methylation

To determine the optimal conditions for the methylation of the benzoyl ether (**2.20**), the conditions for the synthesis of the butanoyl salt (**2.1**) were used as a reference. Specifically, the methylation of the butanoyl salt precursor (**2.28**) requires a temperature of 30 °C and time of 8h to achieve completion, Scheme 2.3.

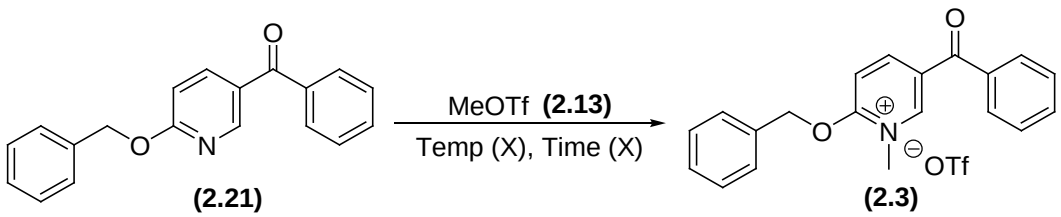
Scheme 2.3: Butanoyl Salt Synthesis



(2.28) **(2.1)** 91%

The requirement for higher temperatures to form the butanoyl salt (**2.1**) suggests a decreased nucleophilic character of the pyridyl nitrogen due to decreased electron density in the ring. With the benzoyl derivative (**2.3**), the decreased electron withdrawing was expected to be not as significant, because of electron donation of the phenyl ring to the carbonyl carbon. A series of trials using 1.15 equiv. MeOTf (**2.13**) and ketone precursor (**2.21**) confirmed this theory as it took significantly less time and a slightly lower temperature of 30 °C to efficiently methylate the precursor (**2.21**) into the corresponding salt (**2.3**), Table 2.8.

Table 2.8: Screening of Temperatures Required for Methylation



(2.21) **(2.3)**

Entry	Temp (°C)	Time (h)	Yield (%)
1	0	1	-
2	23	2	71
3	23	16	91
4	30	1.75	71

With each trial (entries 1-4), MeOTf (**2.12**) was initially added dropwise at 0 °C. the solution in entry 1 was kept at 0 °C for 1h, and precipitation of **2.3** was not observed. In entry 2, the solution was warmed to 23 °C and precipitation did occur. The reaction was allowed to stir for 2h before completion was indicated by TLC, and the precipitate was suspended with hexanes and isolated using vacuum filtration to obtain a 71% yield. Some ether (**2.21**) was found to have not been methylated according to ^{1}H NMR, and another 23 °C reaction (entry 3) was run over 16h to obtain a 91% yield. All the ether was found to be methylated in this extended reaction. Based on the results of entries 2 and 3 the time optimal needed for complete methylation is expected to be between 2h and 16h at 23 °C. In entry 4, the solution was heated to 30 °C after MeOTf (**2.12**) was completely added, and reaction completion was confirmed by TLC at 1.75h. Decomposition with this slight increase in temperature was noted to have occurred based on additional spots appearing on the TLC plate, and peaks associated with the pyridine byproduct were observed in the separated hexanes and toluene by ^{1}H NMR (entry 4).

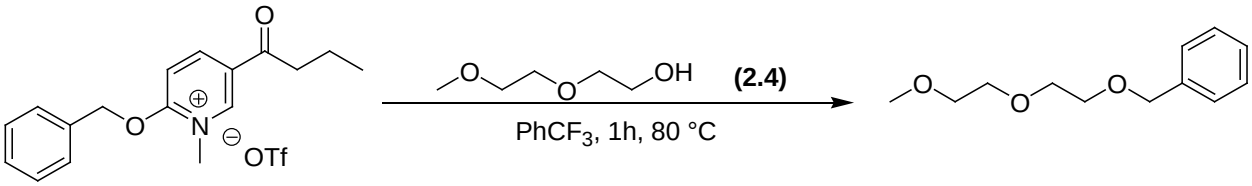
In comparison to the 0 °C conditions used in the methylation of BnOPT, the higher temperature required for the methylation of the benzoyl ether (**2.21**) suggest the pyridyl nitrogen has decreased nucleophilic character. This results from the attached benzoyl group's electron withdrawing nature, and

in turn a higher temperature would be required for methylation to occur[4]; however, the activation energy associated with the decomposition of the salt (**2.3**) would be expected to be lower, due to the electron withdrawing of the benzoyl group, and a benzyl transfer reaction using this salt (**2.3**) would allow for more mild conditions than BnOPT. To determine if more mild conditions were possible for a benzyl transfer reaction using the benzoyl salt (**2.3**), a series of transfer reactions at varying times and temperatures were performed using the salt (**2.3**).

2.6 Transfer Reaction and Byproduct Isolation

Before the benzoyl salt (**2.3**) was synthesized, significant enhanced reactivity with the moderate EWG derivatives was observed with the butanoyl salt (**2.1**). An electrophilic benzyl transfer reaction using the butanoyl derivative (**2.1**) was found to reach completion in 1h as opposed to 24h for BnOPT, and this supports the proposal of the pyridyl leaving group stabilized by the electron withdrawing effect of the butanoyl group. With a 91% yield of the benzyl ether (**2.5**), the derivative was a success in enhancing the reactivity BnOPT salt, and a similar level of reactivity using the benzoyl salt (**2.3**) was sought after, Scheme 2.4.

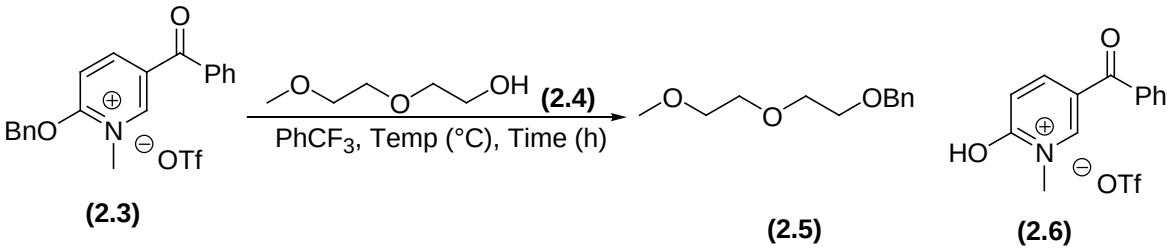
Scheme 2.4: Benzylation using the Butanoyl Derivative



(2.1) **(2.5)** 91%

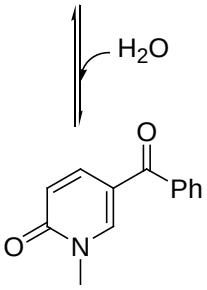
In an investigation of its reactivity, the benzoyl salt (**2.3**) was reacted with an alcohol at three different temperatures and times, Table 2.9.

Table 2.9: Varying Times and Temperatures using the Benzoyl Salt



(2.3) **(2.5)** **(2.6)**

Entry	Time (h)	Temp (°C)	Completion (%)	ROH (%)	Ether (%)	Byproduct (%)
1	4	80	87	13	86	≥99
2	4	80	86	59	78	≥99
3	24	50	31	-	-	-
4	72	23	10	-	-	-



(2.7)

[a.] All the percentages listed are recoveries.

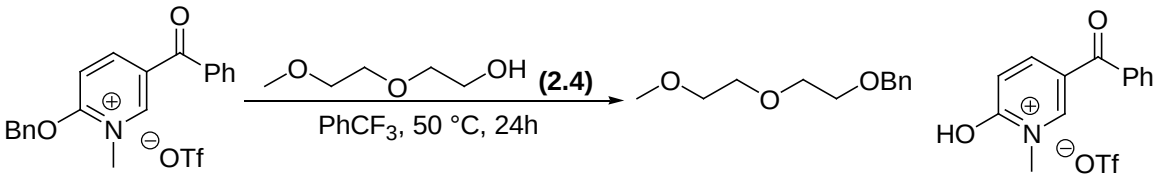
[b.] Completion was determined based on the ratio between the ether's and ROH terminal methyl peaks in an ^{1}H NMR spectra.

[c.] The percentages of the ether and ROH are based on ratio between the recovered mass and the mass possible based on the reaction completion.

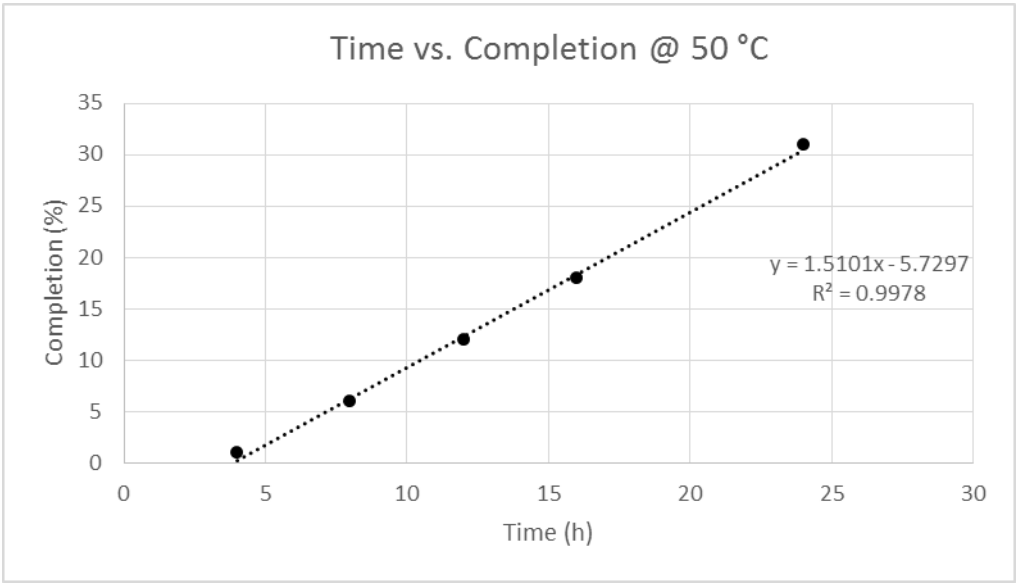
[d.] Recoveries for entries 3 and 4 are not listed, due to the overall crude recovery having too small of mass for purification to be applied.

In the two 80 °C trials (entries 1-2), the reaction reached 86-87% completion within a 4h period. The usage of a diethyl ether trituration was also successful in separating the ether (**2.5**) and left-over alcohol (**2.4**) from the byproduct (**2.7**) with ≥99% isolated (entries 1-2). This trituration was performed using two 2 mL diethyl ether triturations and the obtained ether alcohol mixture was decanted for further purification by column chromatography. The ether (**2.5**) and alcohol (**2.4**) yields were both lower than expected and may have been a result of the 50 mg theoretical yield used. In particular, the difference between the recoveries of entry 1 and entry 2 may have resulted from a loss of a few mg of ether during either isolation or purification in entry 2. In the case of 23 °C and 50 °C (entries 3 and 4), purification was not attempted, due to its already small potential yield of 25 mg. In the 50 °C trial (entry 3); however, insight on the salt's (**2.3**) reactivity was provided through a 24h rate study. NMR aliquots were taken at select times to evaluate the rate of the salt's (**2.3**) decomposition over this 24 h period, Scheme 2.5.

Scheme 2.5: 24h Rate Study at 50 °C



(2.3) **(2.5)** **(2.6)**



The reaction began with a gradual formation of benzyl ether (**2.5**) around 4h, and a rate of 1.51% ether (**2.5**) formation every hour during the experiment. The decomposition of the salt (**2.3**) may have a time threshold at a given temperature where decomposition begins, instead of occurring immediately. If solubility of the salt is greater than BnOPT, the time threshold may have been shortened by greater interaction between the salt and the alcohol. To determine if enhanced solubility played a role in shortening this initial gap in reactivity, other rate studies using BnOPT and its derivatives would need to be performed to see if there is a difference between theirs and benzoyl derivative (**2.3**) time thresholds.

2.7 Conclusion

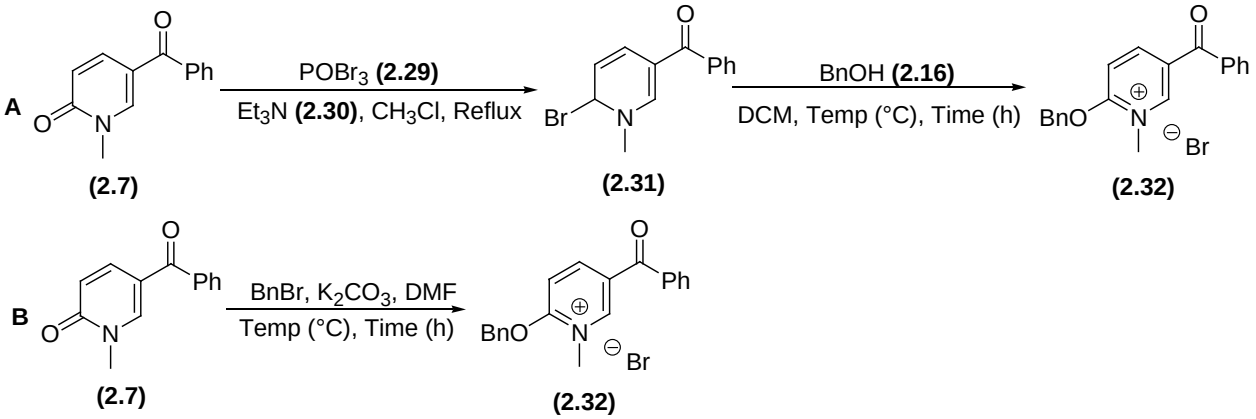
Based on the work presented, the benzoyl derivative (**2.3**) was successfully synthesized following the proposed pathway shown in Figure 2.5, but the steps in the synthesis have yet to be completely optimized. Starting with the initial Grignard addition, the ideal times of reflux for formation of the phenyl Grignard and its addition to **2.17** were determined (entry 7), Table 2.5, but have yet to be applied to a one-pot reaction. In the one-pot reactions performed, 1% sulfuric acid (pH=1.02) was found to be the most effective acid source for hydrolysis providing a 71% yield after purification (entry 3), Table 2.7. The hydrolysis has yet to be optimized as evidence of a pH threshold was observed, Table 2.6, and has yet to be evaluated to both provide a timely hydrolysis and prevent protonation and decomposition of the benzoyl ether (**2.21**). Methylation of **2.21** was found to occur optimally at 23 °C (entries 2 and 3), Table 2.6, but the exact time for a complete methylation has yet to be determined.

Transfer reactions using **2.3** showed the salt's reactivity was greater than BnOPT but less than the other acyl pyridyl derivatives, Table 2.9. An exact time required for completion at 80 °C has not yet been determined, and longer times and a larger excess of salt may be used to achieve reaction completion. The formed byproduct (**2.7**) was successfully isolated in excess of 99% for both 80 °C transfer reactions (entries 1 and 2) using a diethyl ether trituration that was previously evaluated in the isolation studies, Table 2.3 Table 2.4. An exact determination as to whether the solubility of **2.3** was greater than other derivatives has yet to be determined, but rate studies using other derivatives will need to be conducted for comparison for the 24h rate study done using **2.3**, Scheme 2.4. These results ultimately lend credence to the possibility of oxypyridinium salts as tunable electrophiles.

In a future project, a methodology for the reformation of the salt will be developed to complete process of recyclization. Based on existing literature, there appears to be two potential pathways for

salt reformation. One is the byproduct (**2.7**) is halogenated using phosphoryl bromide (**2.29**) at reflux in chloroform to form 2-bromo-5-benzoyl-1-methylpyridone (**2.31**). **2.31** would be reacted with benzyl alcohol in anhydrous DCM at set time and temperature to reform the salt (**2.32**), Scheme 2.6 A.[5] In the second pathway, the benzoyl byproduct (**2.7**) can be directly coupled with benzyl bromide using K_2CO_3 as a base, and DMF as a solvent to reform the salt (**2.32**), Scheme 2.6 B.[6] Both pathways would require an investigation into the ideal time for the salt formation, but pathway **B** would require an investigation into the temperature as well.

Scheme 2.6: Pathways of Benzoyl Salt Reformation Scheme goes over the margin.



In conclusion of this work, it has been determined the reactivity of acyl pyridyl derivatives can be modified using the attached R-group of the ketone. A method of byproduct isolation using diethyl ether trituration has also been determined, which may enable future reformation experiments using the byproducts of BnOPT derivatives.

References

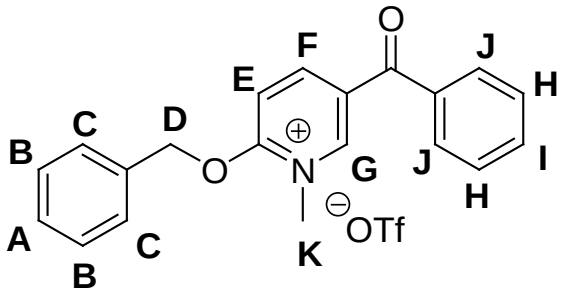
1. Nwoye, E. O.; Dudley, G. B. Synthesis of para-methoxybenzyl (PMB) ethers under neutral conditions. *Chem. Comm.* **2007**, 1436-1437.
2. Kubota, K.; Yamamoto, E.; Ito, H. Correction to "copper(I)-catalyzed borylative exo-cyclization of alkenyl halides containing unactivated double bond". *J. Am. Chem. Soc.* **2015,** *137*, 420-424.
3. Weiberth, F. J.; Hall, S. S., Copper (I)-acitivated addition of grignard reagents to nitriles. Synthesis of ketimines, ketones, and amines. *J. Org. Chem.* **1987,** *52*, 3901-3904.
4. Bakshi, T. Substituent effects on the synthesis and reactivity of 2-benzyloxypyridiniun triflate derivatives. Ball State, 2014.
5. Munyemana, F.; George, I.; Devos, A.; Colens, A.; Badarau, E.; Frisque-Hesbin, A.; Loudet, A.; Differding, E.; Damien, J.; Remion, J.; Uytbergen, J.; Ghosez, L., A mild method for the replacement of a hydroxyl group by halogen. 1. Scope and chemeoselectivity. *Tetrahedron* **2016,** *72*, 420-430.
6. Bommagani, S.; Lee, N.; Zhang, X.; Dwoskin, L.; Zheng, G., Synthesis of *O*- and *N*-alkylated product of 1,2.3,4-tetrahydrobenzo [c][2,7]naphthyrin-5(6*H*)-one. *Tetrahedron Lett* **2015,** *56*, 6472-6474.

Chapter 3
Experimental

General information:

Chemicals were purchased from Sigma-Aldrich, Spectrum, Acros, or Ark Pharma and used without further purification unless otherwise noted. All glassware, glass syringes, stir bars, and needles were dried in an oven at 110 °C for 24h, and transferred and cooled in a desiccator prior to use. Reactions were performed using a double manifold under an argon atmosphere. Silicon grease was added to the joints of flasks subjected to heating. TLC plates from Sorbent Technologies (Aluminum back, Silica gel, UV 254, 20 μm) were used to monitor reactions for completion. A UV (254 nm) lamp, p-anisaldehyde stain (6 g anisaldehyde, 250 ml Ethanol, 2.5 ml conc. H_2SO_4), or KMnO4 stain (1 g $KMnO_4$, 6.5 g K_2CO_3, 2 ml of 5% NaOH, 100 ml H_2O) were used to visualize compounds on TLC plates. Toluene and α, α, α-trifluorotoluene were distilled and stored under argon in an amber bottle over molecular sieves. Flash column chromatography with Dynamic Adsorbents flash silica gel (32-63 μm) was used for purification of products. Molecules were characterized by ^{1}H and ^{13}C NMR using a JEOL 300 MHz or 400 MHz instrument. Chloroform-D (D, 99.8% + 0.05% V/V TMS) from Cambridge Isotope Laboratories was used as the solvent for all NMR spectra. Attenuated total reflection (ATR) was the sampling technique used in conjunction with IR spectroscopy on a Perkin Elmer Spectrum 100 FT-IR instrument to acquire IR spectra.

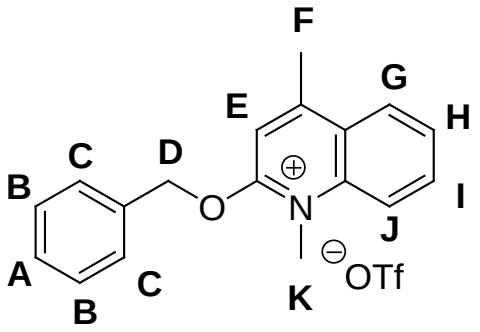
Synthetic Procedures



2.3

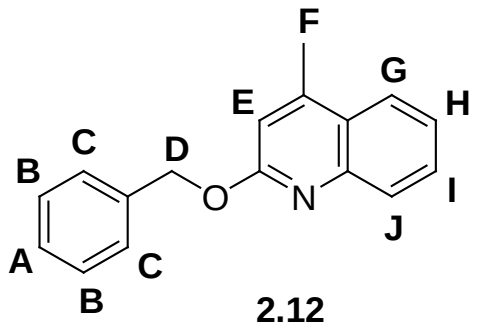
2-Benzyloxy-5-benzoyl-1-methylpyridinium triflate. (SED_II_14). An oven dried, single neck 10-mL round bottom flask was charged with 2-benzyloxy-5- benzoyl pyridine (0.0921 g, 0.318 mmol), toluene (0.3 mL), and a stir bar, and the system was placed under an argon atmosphere with stirring. The flask was cooled to 0 °C in an ice bath, and after equilibration MeOTf (0.040 mL, 0.366 mmols) was added dropwise over 10 min. Upon complete addition, the reaction mixture was allowed to warm to RT. The reaction was found to be complete by TLC after stirring for 2h. The white, granular precipitate was

isolated with vacuum filtration, rinsed with hexanes, and dried under vacuum overnight to obtain a white, powdery solid. (0.1016 g, 0.224 mmol, 71 %). Melting point: 80-82 °C, ^{1}H NMR (400 MHz, CD_3Cl) δ 8.64 (dd, *J* = 9.2 Hz, 2.0 Hz, $1H_F$), 8.54 (d, *J* = 1.6 Hz, $1H_G$), 7.93-7.92 (m, $2H_J$), 7.61-7.65 (m, $2H_{E,I}$), 7.71-7.65 (m, $4H_{B,H}$), 7.47-7.46 (m, $3H_{A,C}$), 5.72 (s, $2H_D$), 4.17 (s, $3H_K$). IR (FTIR, cm^{-1}) 3082 (C-H stretching), 1663 (C=O stretching (conjugated ketone)), 1633 (C=C stretching), 1449 (C-H stretching (methyl group)), 1390 (C-N stretching), 1145 (C-O stretch), 741 (C-H bending).



2.8

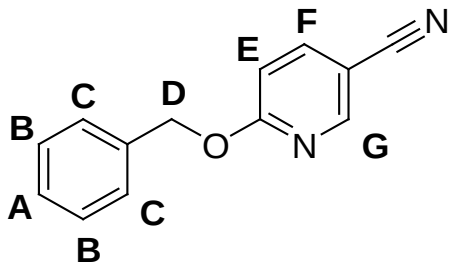
2-Benzyloxy-1-methyllepidinium triflate. (**SED_I_54**). An oven dried, two neck, 25-mL round bottom flask was charged with 2-benzyloxy lepidine (0.1587 g, 0.637 mmol), toluene (0.6 mL), stir bar, and the system was placed under argon atmosphere with stirring. The flask was cooled to 0 °C in an ice bath, and after equilibration MeOTf (0.150 mL, 1.39 mmol) was added dropwise over 10 min. Upon completion, the reaction mixture was allowed to warm to RT. The reaction was found to be complete by TLC after stirring for 3h. The white, granular precipitate was isolated with vacuum filtration, rinsed with hexanes, and dried under vacuum overnight to obtain a white, powdery solid. The white, granular solid was dried under vacuum, placed under an argon atmosphere, and placed in refrigeration for long term storage. (0.2144 g, 0.517 mmol, 86%). Melting point: 107-108 °C, ^{1}H NMR (400 MHz, CD_3Cl) δ 8.19 (d, *J* = 8.0 Hz, $1H_G$), 8.06-7.99 (m, $2H_{H,I}$), 7.85 (s, $1H_E$), 7.77 (dt, *J* = 6.4, 1.6 Hz, $1H_J$), 7.58-7.56 (m, $2H_c$), 7.44-7.42 (m, $3H_{A,B}$), 5.86 (s, $2H_D$), 4.21 (s, $3H_K$), 2.98 (s, $3H_F$). ^{13}C NMR (100 MHz, CD_3Cl) δ 160.0, 159.9, 137.3, 135.2, 132.8, 129.6, 129.1, 128.9, 127.7, 126.6, 124.3, 122.5, 120.9 (q, J_{C-F} = 319.8), 119.3, 117.8, 110.2, 75.5, 34.1, 20.2. IR (FTIR, cm^{-1}) 3085 (C-H stretching (alkene)), 1611 (C=C stretching), 1459 (C-H bending (methyl group)), 1371 (C-N stretching), 1262 (C-O stretch), 980 (C=C bending), 759 (C-H bending).



2.12

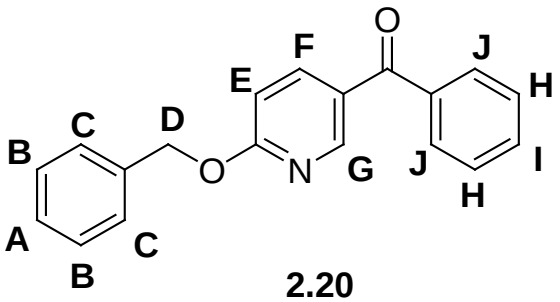
2-Benzyloxylepidine. (SED_I_43) An oven dried, two neck 50-mL round bottom flask charged with a reflux condenser, and 2-chlorolepidine (0.7130 g, 4.01 mmol), benzyl alcohol (0.5174 g, 4.78 mmol),

potassium hydroxide (0.7935 g, 14.1 mmol), toluene (4 mL), a stir bar, and the system was placed under an argon atmosphere with stirring. The solution was then refluxed (115 °C), and the reaction was found to be complete by TLC at 6h. The recovery was isolated into a separatory funnel with dichloromethane (10 mL) and washed with water (10 mL) and brine (10 mL). The organic layer was transferred to an Erlenmeyer flask and dried over with anhydrous sodium sulfate. Vacuum filtration was used to separate the recovery from the sodium sulfate, and the recovery was collected in a pre-weighed round bottom flask. The recovery was purified using 19:1 hexanes to EtOAc eluent in column chromatography, and the concentrated eluent provided a white, granular solid (0.8767 g, 3.52 mmol, 87%). Melting point: 43-44 °C, ^{1}H NMR (400 MHz, CD_3Cl) δ 7.89-7.86 (m, $2H_{I,G}$), 7.65-7.61 (m, $1H_A$), 7.53-7.51 (m, $2H_{H,J}$), 7.43-7.37 (m, $3H_B$), 7.34-7.31 (m, $1H_C$), 6.83 (s, $1H_E$), 5.54 (s, $2H_D$), 2.63 (s, $3H_F$). ^{13}C NMR (100 MHz, CD_3Cl) δ 162.0, 147.1, 146.9, 137.9, 129.6, 128.8, 128.6, 128.2, 128.1, 125.8, 124.2, 124.0, 67.7, 18.8. IR (FTIR, cm^{-1}) 3063 (C-H stretching), 3033 (C-H stretching), 1947 (C-H bending aromatic), 1611 (C=C stretching), 1471 (C-H bending (methyl group)), 1334 (C-N stretching), 752 (C-H bending).



2.17

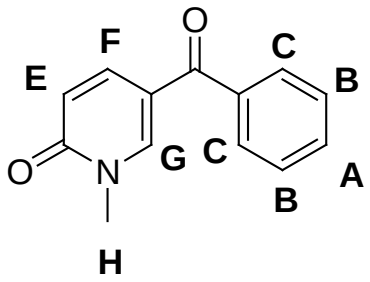
2-Benzyloxy-5-cyanopyridine. (**SED_I_51**) An oven dried, three neck 50-mL round bottom flask charged with 2-chloro-5-cyano pyridine (0.3298 g, 2.38 mmol), benzyl alcohol (0.2800 g, 2.59 mmol), potassium hydroxide (0.5173 g, 9.22 mmol), trifluorotoulene (2.4 mL), glass stoppers, and a stir bar before the system was placed under an argon atmosphere with stirring at RT. The reaction was monitored with TLC to determine its completion at 6h. The solution was transferred to a separatory funnel with dichloromethane (20 mL) and washed with water (20 mL) and brine (20 mL). The organic layer was transferred to an Erlenmeyer flask and dried over with anhydrous sodium sulfate. Vacuum filtration was used to separate the recovery from the sodium sulfate, and the recovery was collected in a pre-weighed round bottom flask. The recovery was subsequently concentrated down on a rotary evaporator. The resulting white, crystalline solid was then subsequently recrystallized using hexanes (15 mL) for purification to obtain another white crystalline powder. (0.4057 g, 1.93 mmol, 81 %). Melting point: 67-69 °C, ^{1}H NMR (400 MHz, CD_3Cl) δ 8.51 (d, *J* = 2.0 Hz, $1H_G$), 7.80 (dd, *J* = 8.8, 2.4 Hz, $1H_F$), 7.46-7.34 (m, $5H_{A,B,C}$), 6.87 (d, *J* = 8.4 Hz, $1H_E$), 5.44 (s, $2H_D$). ^{13}C NMR (100 MHz, CD_3Cl) δ 165.5, 152.0, 141.2, 136.2, 128.7, 128.4, 128.3, 117.4, 112.2, 102.7, 68.8. IR (FTIR, cm^{-1}) 3061 (C-H stretching), 2226 (CΞN stretch (nitrile)), 1947 (C-H bending (aromatic)), 1651 (C=C stretching), 1362 (C-N stretching), 1010 (C-O stretch), 727 (C-H bending).



2.20

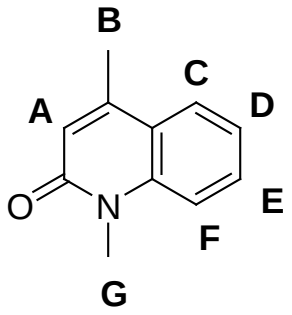
2-Benzyloxy-5-benzoylpyridine. (SED_I_79). A flame dried, two neck 25-mL round bottom flask charged with magnesium turnings (0.1268 g, 5.26 mmol), THF (2 mL), ethylene bromide (1 drop), and stir bar was sealed with a greased condensing column and glass cap before the system was placed under an argon atmosphere with stirring. The solution was cooled to 0 °C with an ice bath, and bromobenzene (0.8136 g, 5.18 mmol) diluted in 1 mL of THF was added dropwise along with a 1 mL THF rinse to the solution. The solution was then warmed to room temperature, and then refluxed at 85 °C for 1.5h using an oil bath. The solution was then cooled to 0 °C before 2-benzyloxy-5-cyanopyridine (0.7385 g, 3.46 mmol) dissolved in 1 mL THF was added drop over ten mins followed by 1 mL THF rinse. Cu(I)Cl (0.0083 g, 0.0838 mmol) was added, and the solution was refluxed at 85 °C for 3h. The solution was then cooled to 0 °C before 2 mL 5% acetic acid solution were added drop wise over 20 min. The solution was stirred for 16 h, and the recovery was isolated using of 20 mL DCM and 20 mL water. The organic layer was transferred to an Erlenmeyer flask and dried over with anhydrous sodium sulfate. Vacuum filtration was used to separate the recovery from the sodium sulfate, and the recovery was collected in a pre-weighed round bottom flask. The recovery was subsequently concentrated down on a rotary evaporator. The recovery was purified a 19:1 hexanes to EtOAc eluent in column chromatography to obtain a clear liquid after concentrating the eluent down by rotovap. (0.6764, 2.34 mmol, 68%). ^{1}H NMR (400 MHz, CD_3Cl) δ 8.64 (d, *J* = 1.6 Hz, $1H_G$), 8.12 (dd, *J* = 8.4, 2.4 Hz, $1H_F$), 7.79 (d, *J* = 7.2 Hz, $2H_J$), 7.61 (t, *J* = 7.6 Hz, $1H_I$), 7.52-7.47 (m, $4H_{B,H}$), 7.42-7.33 (m, $3H_{A,C}$), 6.90 (d, *J* = 8.4 Hz, $1H_E$), 5.48 (s, $2H_D$). ^{13}C NMR (100 MHz, CD_3Cl) δ 194.3, 166.0, 150.9, 140.3, 137.6, 136.7, 132.7, 129.9, 128.7, 128.6, 128.3, 128.2, 127.2, 111.4, 68.5. IR (FTIR, cm^{-1}) 3032 (C-H stretching), 2198 (C-H bending aromatic), 1653 (C=O stretching (conjugated ketone)), 1595 (C=C stretching), 1352 (C-N stretching), 1122 (C-O stretch), 695 (C-H bending).

Compound Isolations and Purifications



2.7

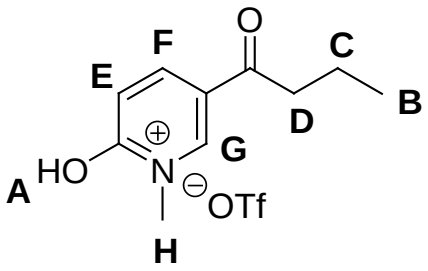
5-Benzoyl-1-methylpyridone. (SED_II_11) A oven dried, 10-mL round bottom was charged with 2-benzyloxy-5-benzoyl-1-methylpyridinium triflate (0.1331 g, 0.293 mmol), 2-(2-methoxyethoxy) ethanol (0.0293 g, 0.244), trifluorotoluene (0.8 mL), and a stir bar before the system was sealed with a greased condensing column, stopper, placed under an argon atmosphere with stirring. The mixture was heated at 80 °C for 4h, and the recovery was isolated into a separatory funnel with dichloromethane (10 mL) and washed with water (10 mL). The organic layer was transferred to an Erlenmeyer flask and dried over with anhydrous sodium sulfate. Vacuum filtration was used to separate the recovery from the sodium sulfate, and the solution was separated into a pre-weighed round bottom flask using vacuum filtration and concentrated down using a rotary evaporator. The obtained brown granular solid was triturated with two 2 mL diethyl ether triturations to obtain a clear crystalline solid (0.0544 g, 0.260 mmol, ≥99%). Melting point: 180-182 °C, ^{1}H NMR (400 MHz, CD_3Cl) δ 8.01 (d, *J* = 2.4 Hz, $1H_G$), 7.90 (dd, *J* = 9.2 Hz, 2.4 Hz, $1H_F$), 7.70 (d, *J* = 8.0 Hz, $2H_C$), 7.61 (t, *J* = 7.2 Hz, $1H_A$), 7.53-7.49 (m, $2H_B$), 6.61 (d, *J* = 9.2 Hz, $1H_E$), 3.610 (s, $3H_H$). ^{13}C NMR (100 MHz, CD_3Cl) δ 191.9, 162.8, 145.2, 139.4, 137.3, 132.4, 129.1, 128.7, 119.6, 117.4, 38.5. IR (FTIR, cm^{-1}) 3058 (C-H stretching), 1902 (C-H bending (aromatic)), 1661 (C=O stretching (conjugated ketone)), 1628 (C=O stretching (amide)), 1431 (C-H stretching (methyl group)), 1376 (C-N stretching), 954 (C=C bending).



2.10

***N*-methyllepidone. (SED_I_55)** An oven dried, two neck 25-mL round bottom flask was charged with 2-benzyloxy-1-methyl lepidine (0.4158 g, 1.00 mmol), 2-(2-methoxyethoxy) ethanol (0.1069 g, 0.890 mmol), magnesium oxide (0.0405 g, 1.00 mmol), trifluorotoulene (3 mL), and a stir bar before the flask was sealed with a greased condensing column, glass stopper, placed under argon with stirring. The solution was heated at 83 °C, and the solution was tested periodically by TLC to determine its completion at 20h. The solution was transferred to a separatory funnel with dichloromethane (20 mL) and washed with water (20 mL). The organic layer was transferred to an Erlenmeyer flask and dried over with anhydrous sodium sulfate. Vacuum filtration was used to separate the recovery from the sodium sulfate, and the recovery was collected in a pre-weighed round bottom flask. The recovery was concentrated down on a rotary evaporator, and an initial attempt at purification using column chromatography was performed, however, separation was not successful. The recovery was triturated using two 2 mL of diethyl ether, and the resulting white solid was dried under high vac. (0.1283 g, 0.741 mmol, 74%). Melting point: 127-128 °C, ^{1}H NMR (400 MHz, CD_3Cl) δ 7.72 (dd, *J* = 8.4, 1.6 Hz, $1H_C$), 7.60-7.56 (m, $1H_E$), 7.38 (d, *J* = 8.0 Hz, $1H_F$), 7.29-7.25 (m, $1H_D$), 6.61 (s, $1H_A$), 3.72 (s, $3H_G$), 2.48 (s, $3H_B$). ^{13}C NMR (100 MHz, CD_3Cl) δ 162.2, 146.5, 139.9, 130.5, 125.3, 122.0, 121.5, 121.1, 114.5, 29.3, 19.1. IR

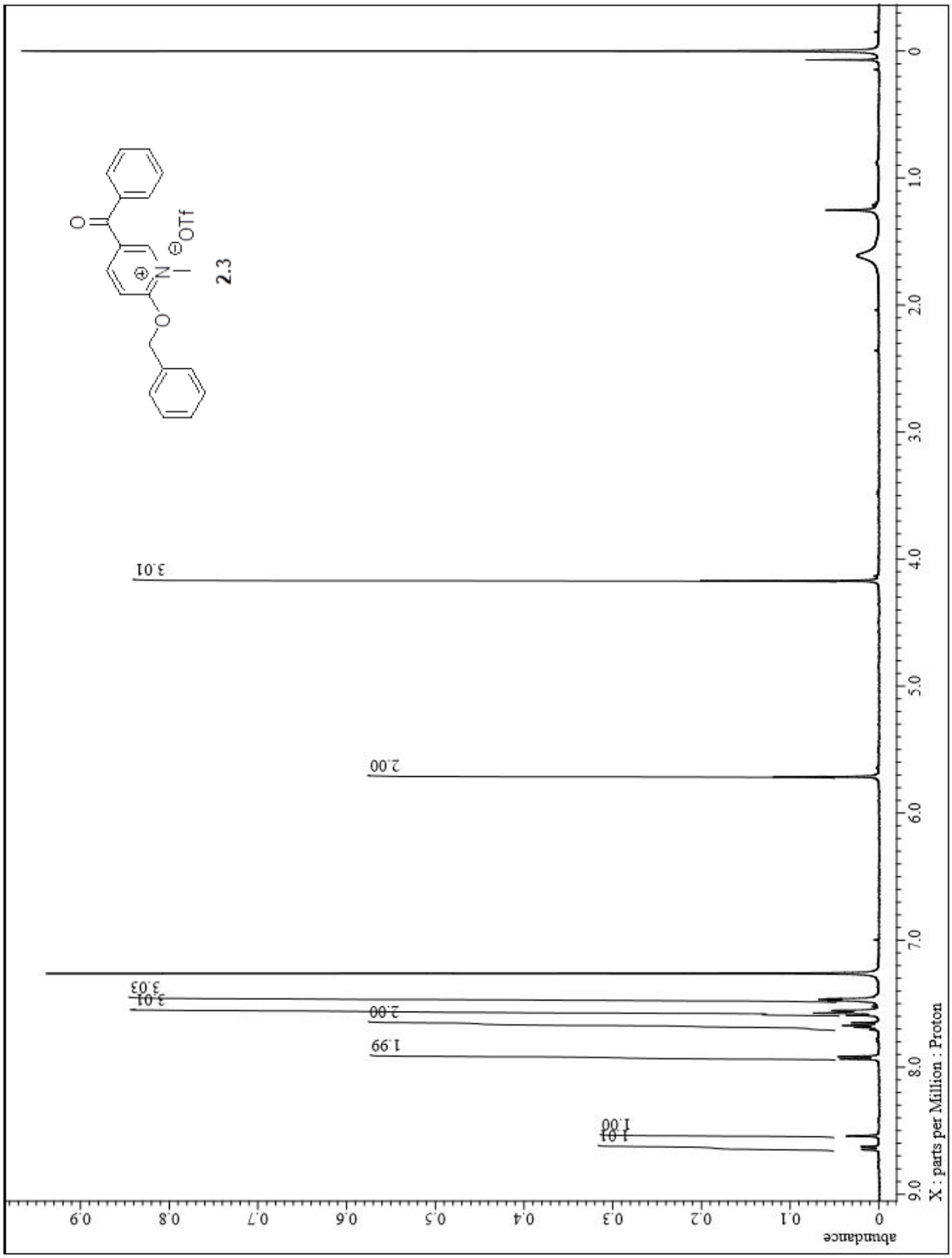
(FTIR, cm^{-1}) 3049 (C-H stretching (alkene)), 1983 (C-H bending aromatic), 1720 (C=C stretching), 1640 (C=O stretching (amide)), 1453 (C-H bending (methyl group)), 1370 (C-N stretching), 923 (C=C bending).



2.11

2-Hydroxy-5-butanoyl-1-methylpyridone. (SED_I_18). A 5-mL vial was charged with 0.0192 g of decomposed 2-benzyloxy-5-oxopropyl-1-methyl pyridinium triflate and diethyl ether (20 mL). The solution was stirred by hand, and the resulting brown crystalline solid was separated from the diethyl ether with vacuum filtration. The solid was then dried under vacuum (0.0150 g, 0.0476 mmol, %). Melting point: 117-118 °C, ^{1}H NMR (400 MHz, CD_3Cl) δ 8.38 (s, $1H_G$), 8.24 (d, *J* = 9.6 Hz, $1H_F$), 7.15 (d, *J* = 8.5 Hz, $1H_E$), 3.86 (s, $3H_H$), 3.04 (s, $1H_A$), 2.84 (t, *J* = 7.2 Hz, $2H_D$), 1.72 (sextet, *J* = 7.2 Hz, $2H_C$), 1.01 (t, *J* = 7.2 Hz, $3H_B$). ^{13}C NMR (100 MHz, CD_3Cl) δ 195.5, 163.5, 143.1, 141.0, 121.9, 121.6, 120.3 (q, J_{C-F} = 319.8 Hz), 118.7, 117.5, 40.4, 39.8, 17.4, 13.7. IR (FTIR, cm^{-1}) 3037 (C-H stretching), 1694 (C=C stretching), 1468 (C-H bending (methyl group)), 1416 (O-H bending), 1333 (C-N stretching), 1254 (C-O stretch), 1029 (O-H stretching).

Appendices A: Supporting Information for the Synthesized Compounds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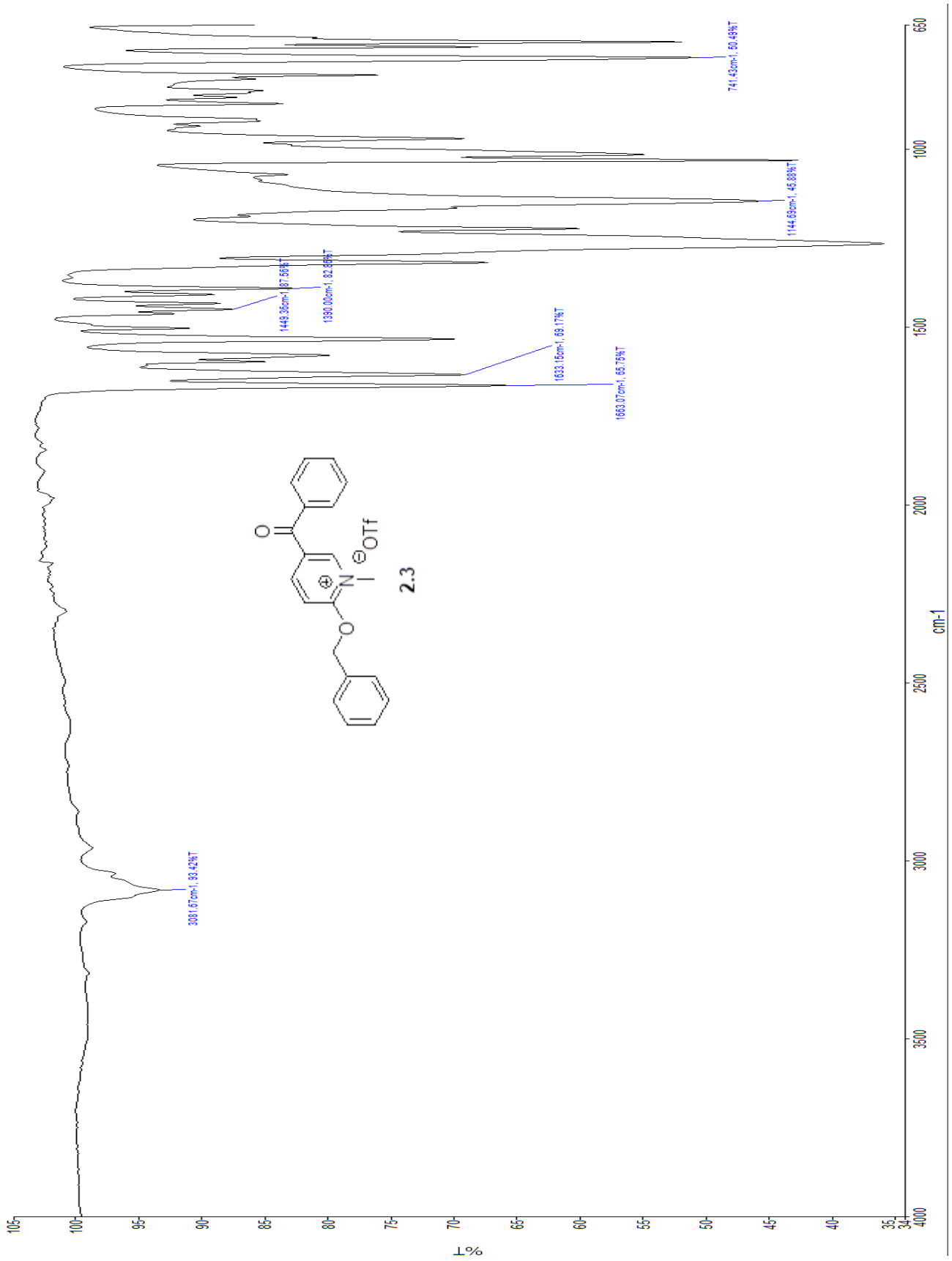
3.01
2.00
1.99
1.00
X : parts per Million : Proton
abundance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1633.16cm-1, 69.17%T
1449.36cm-1, 87.56%T
1390.00cm-1, 82.46%T
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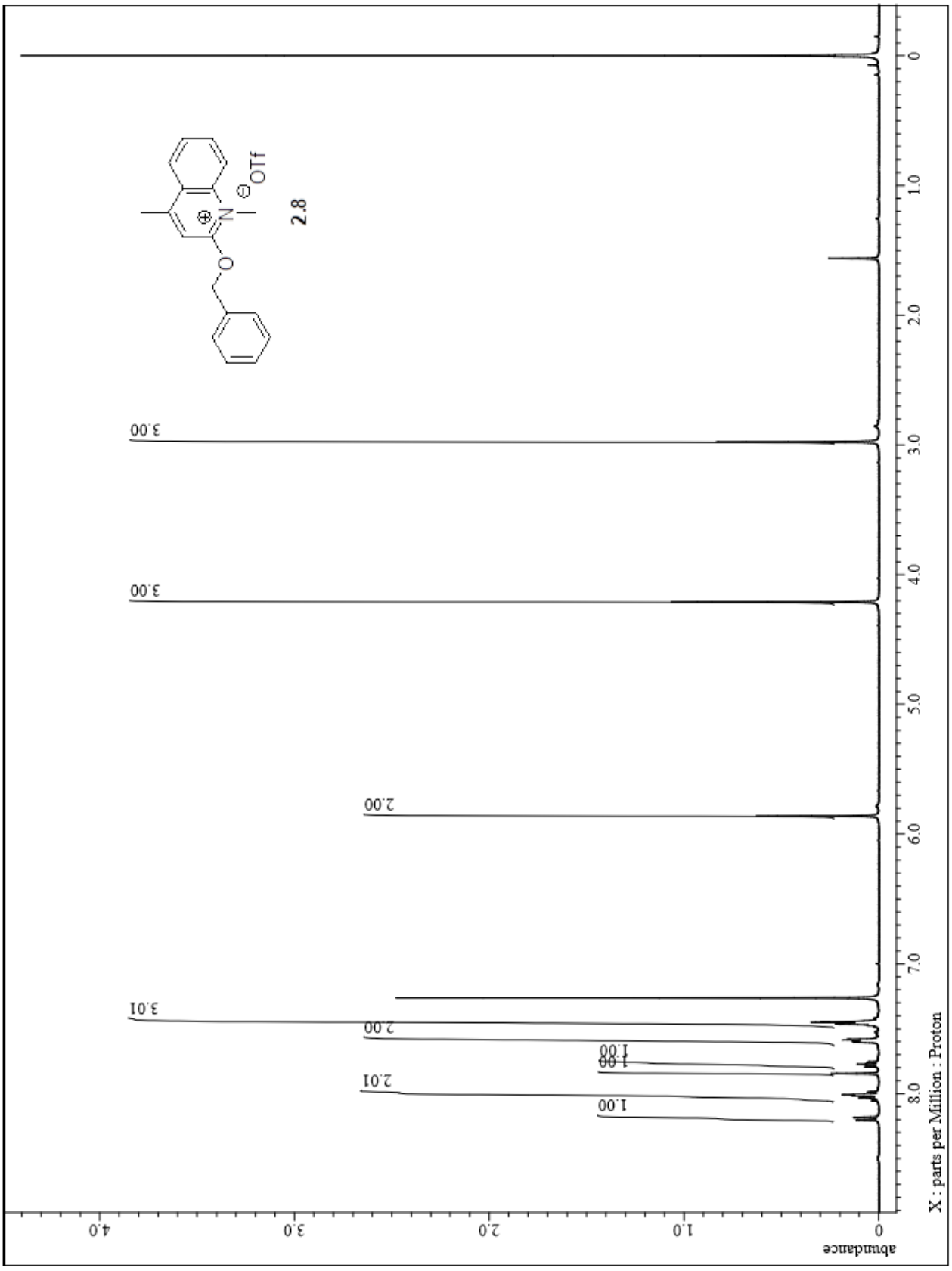
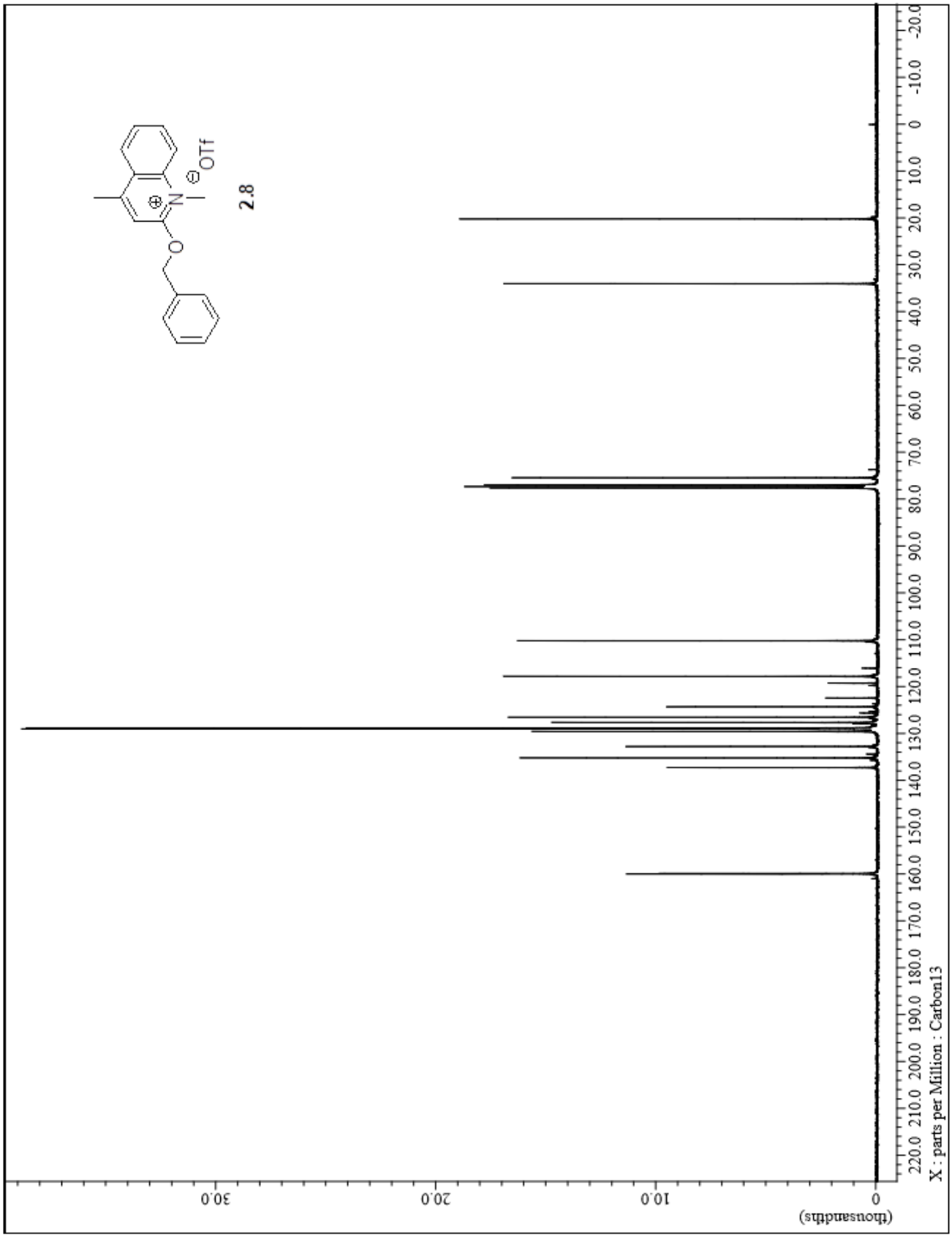
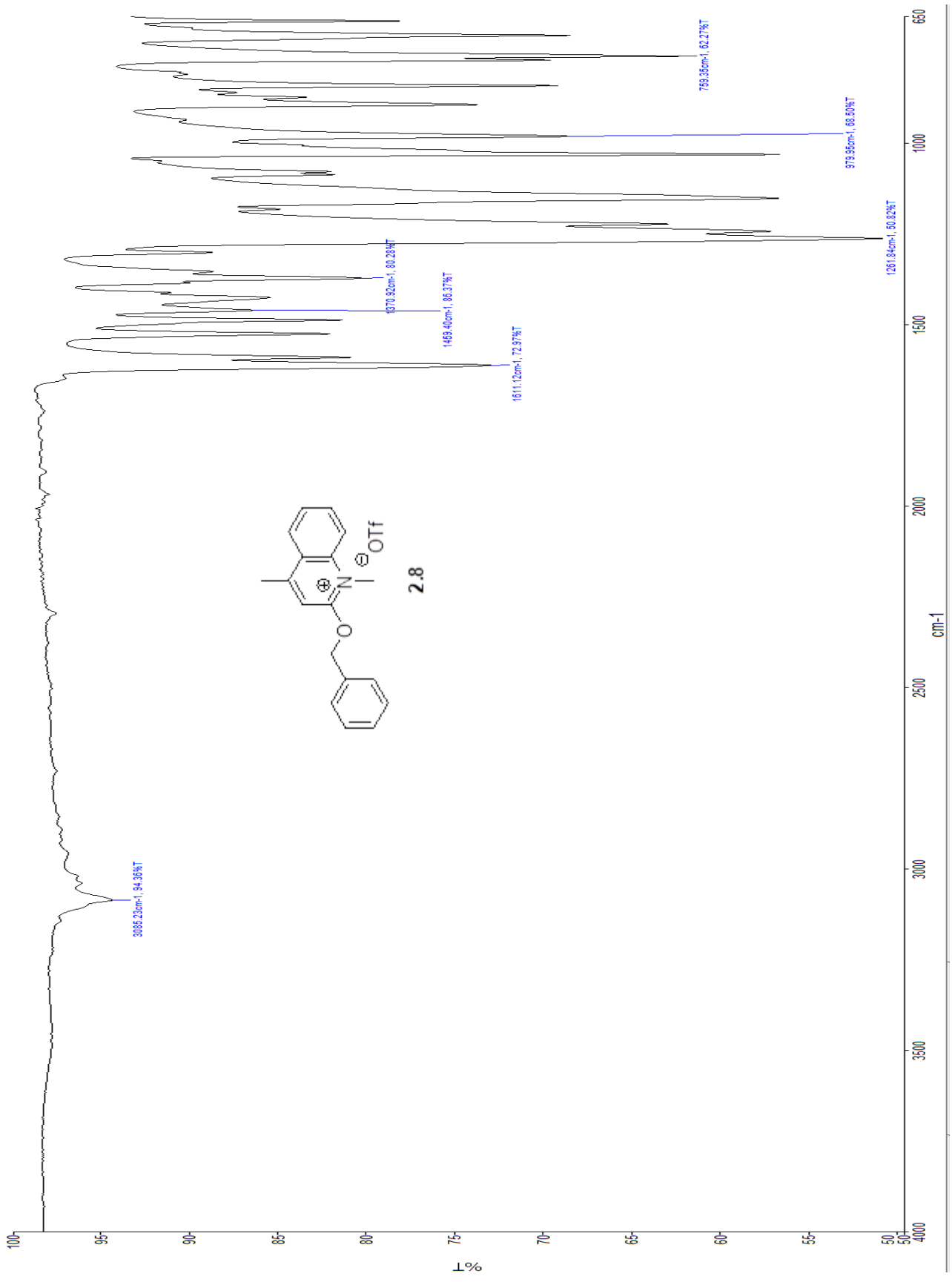
O
OTf
2.3
%T
cm-1


2.8
OTf
3.00
3.00
2.00
3.01
2.00
1.00
1.00
2.01
1.00
X : parts per Million : Proton
abundance


2.8
OTf
(thousandths)
X : parts per Million : Carbon13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1611.12cm-1, 72.97%T
1469.40cm-1, 86.37%T
1370.92cm-1, 80.28%T
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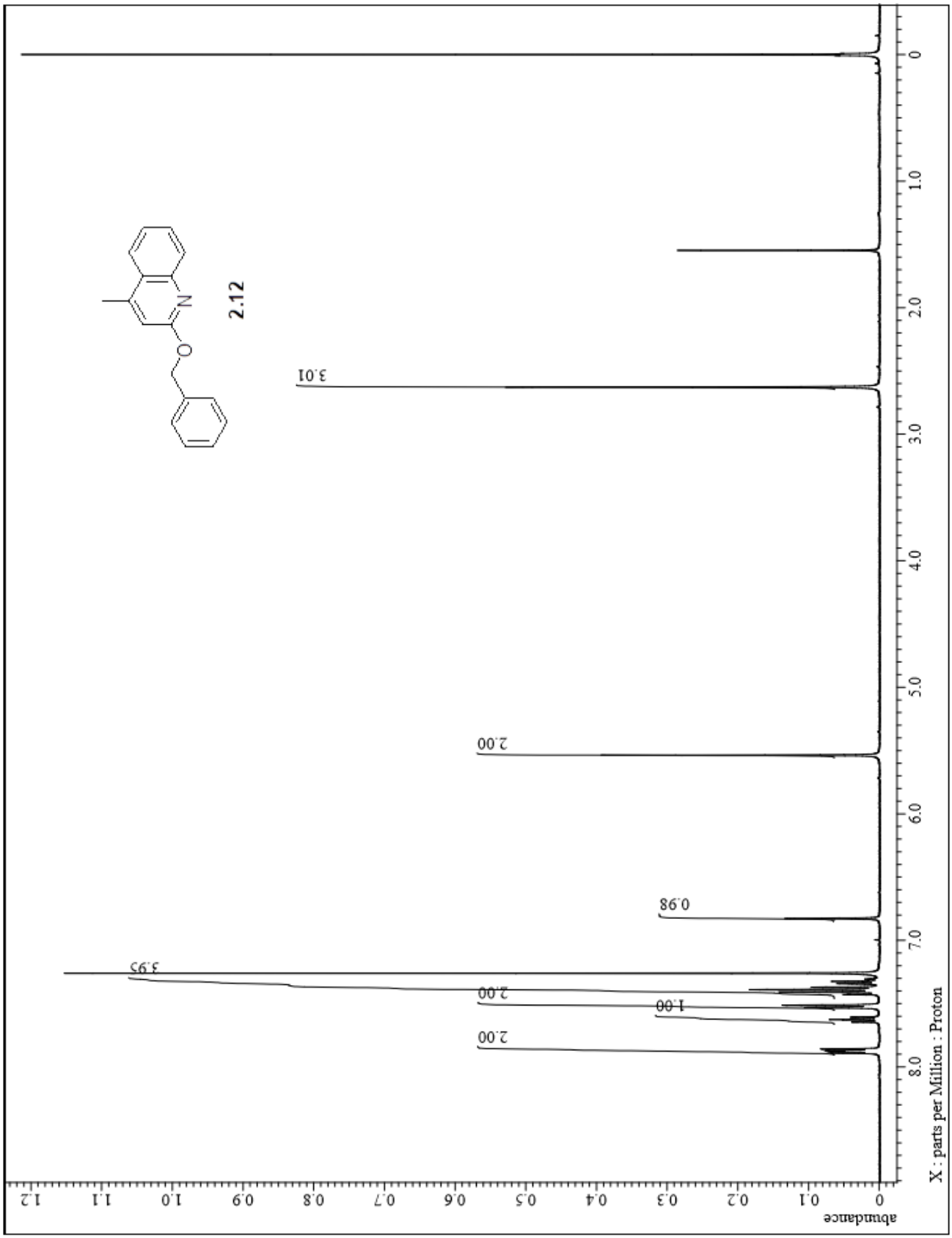
979.95cm-1, 68.60%T
759.36cm-1, 62.27%T
%T
cm-1
OTf
2.8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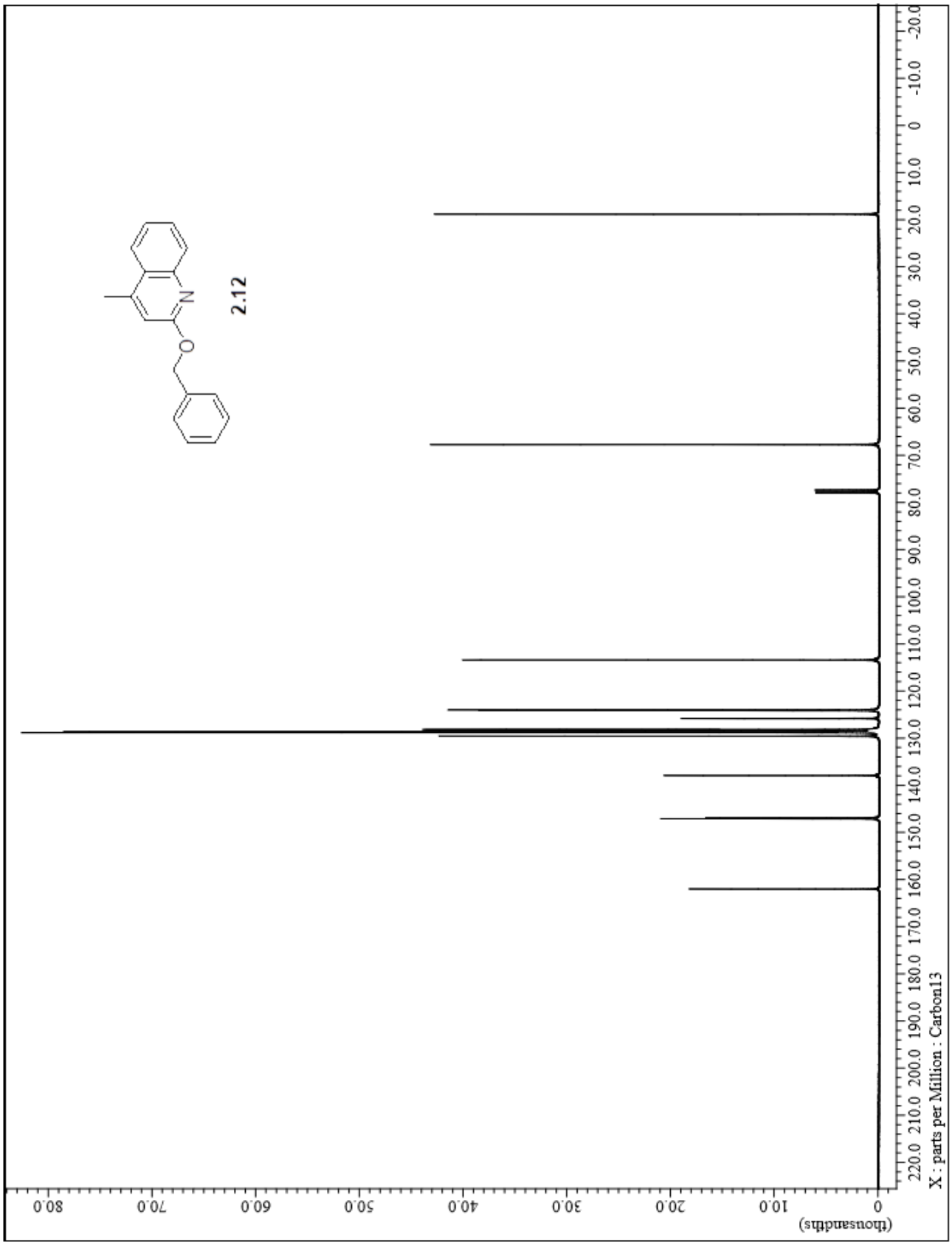
1.00
2.00
X : parts per Million : Proton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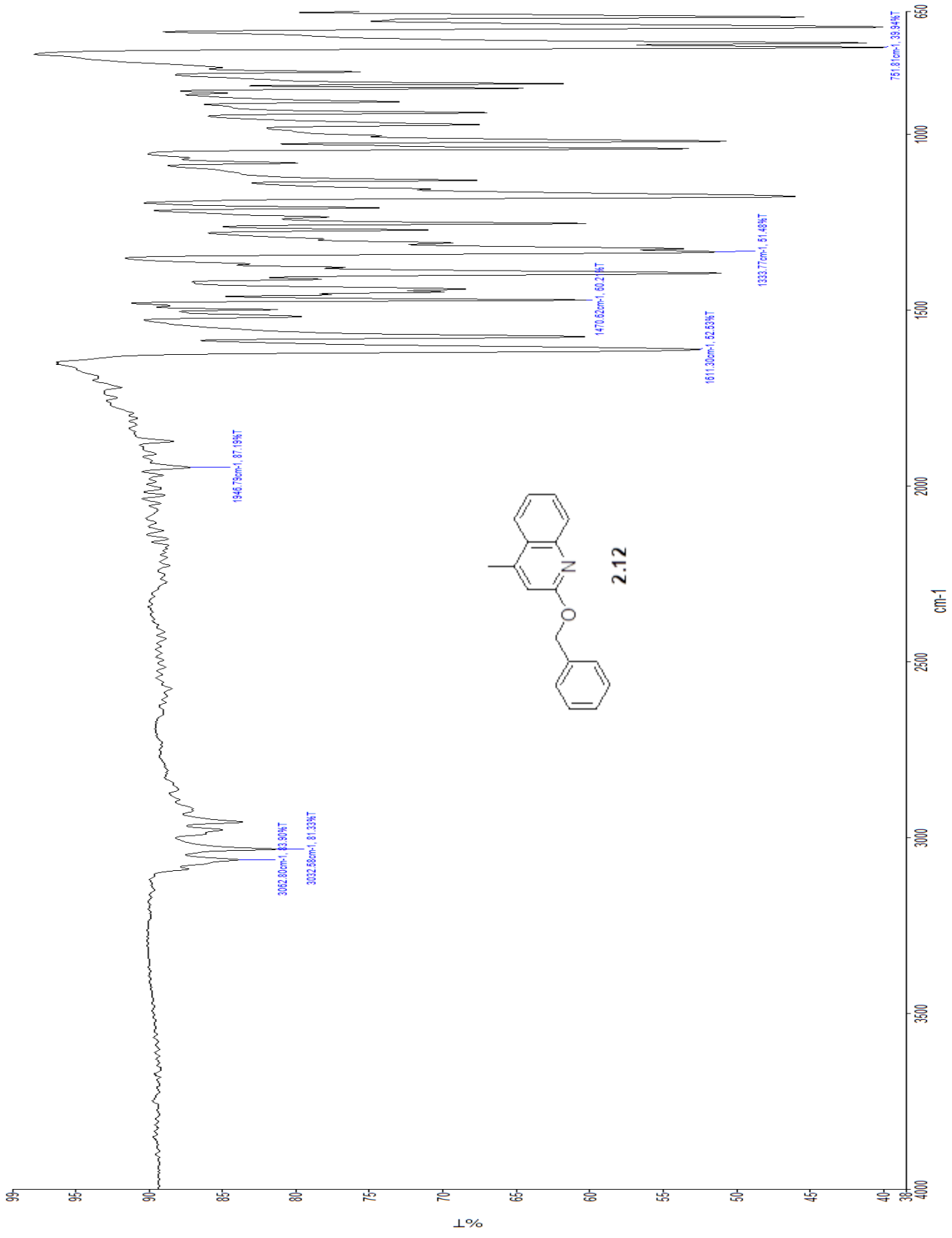
N
O
(thousandths)
X : parts per Million : Carbon13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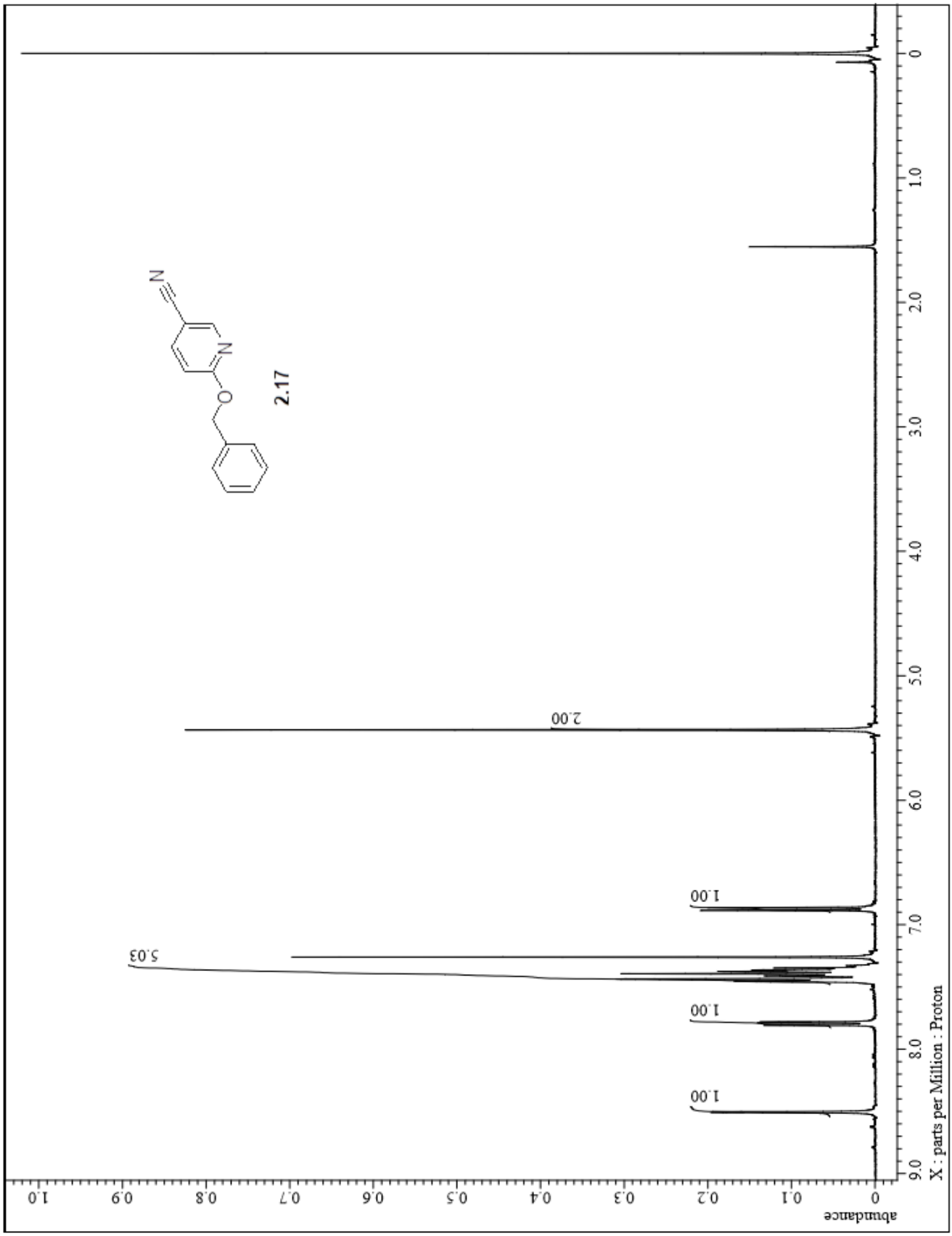
1333.77cm-1, 51.49%T
1470.62cm-1, 60.21%T
1611.30cm-1, 62.53%T
1946.79cm-1, 87.19%T
3062.80cm-1, 83.90%T
3032.68cm-1, 81.33%T
2.12
%T
cm-1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N
N
O
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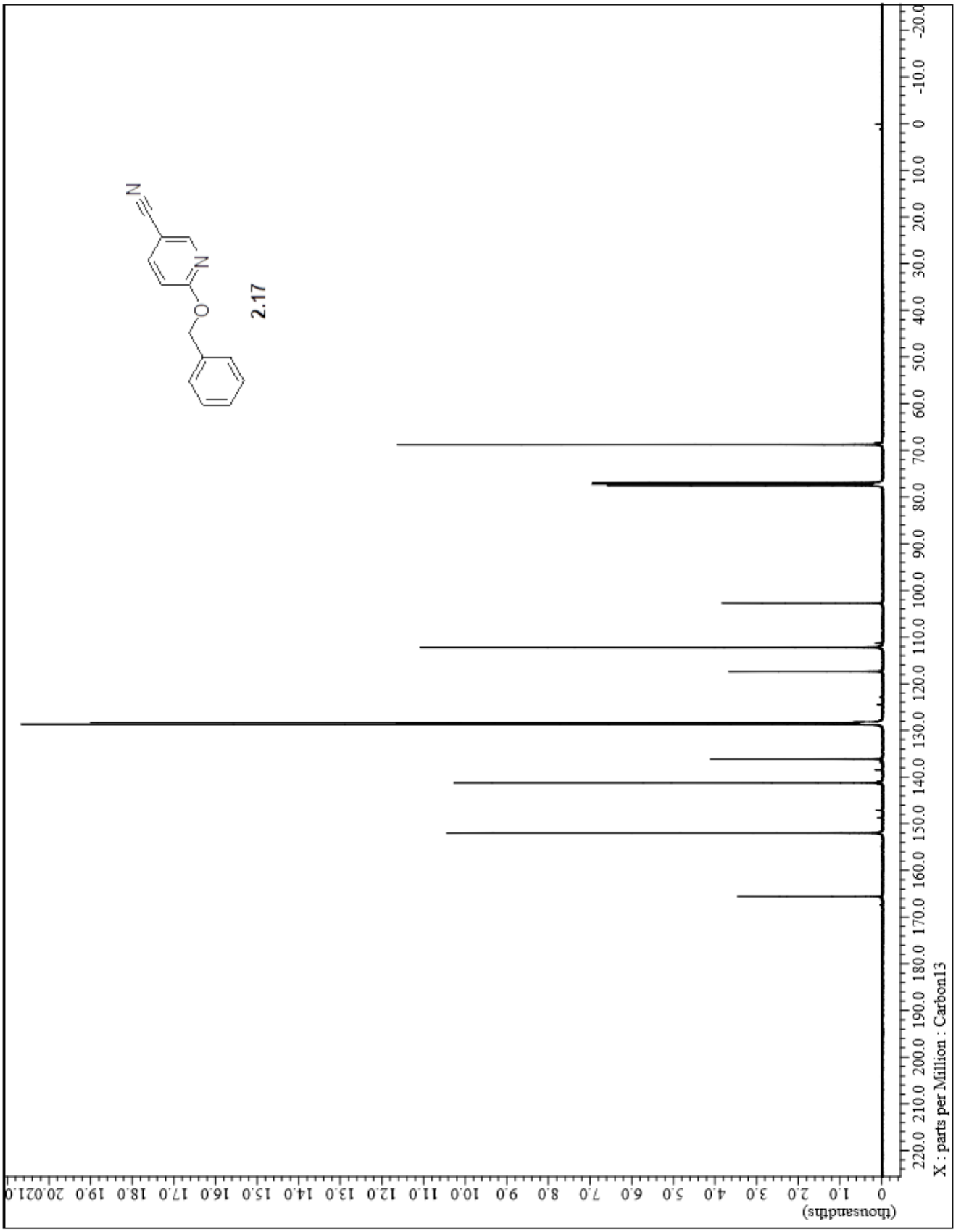
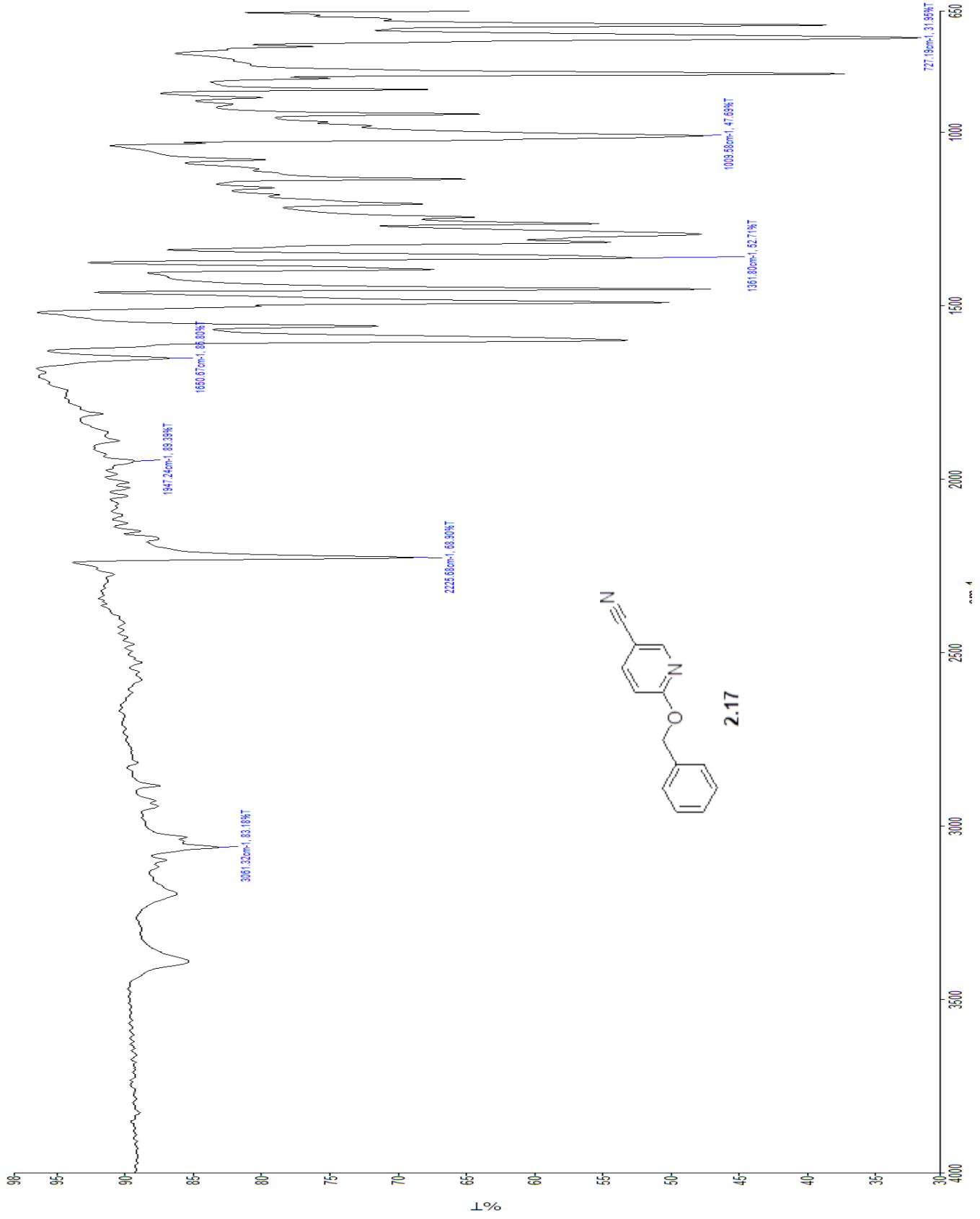
5.03
1.00
2.00
abundance
X : parts per Million : Proton


N
N
O
2.17
(thousandths)
X : parts per Million : Carbon13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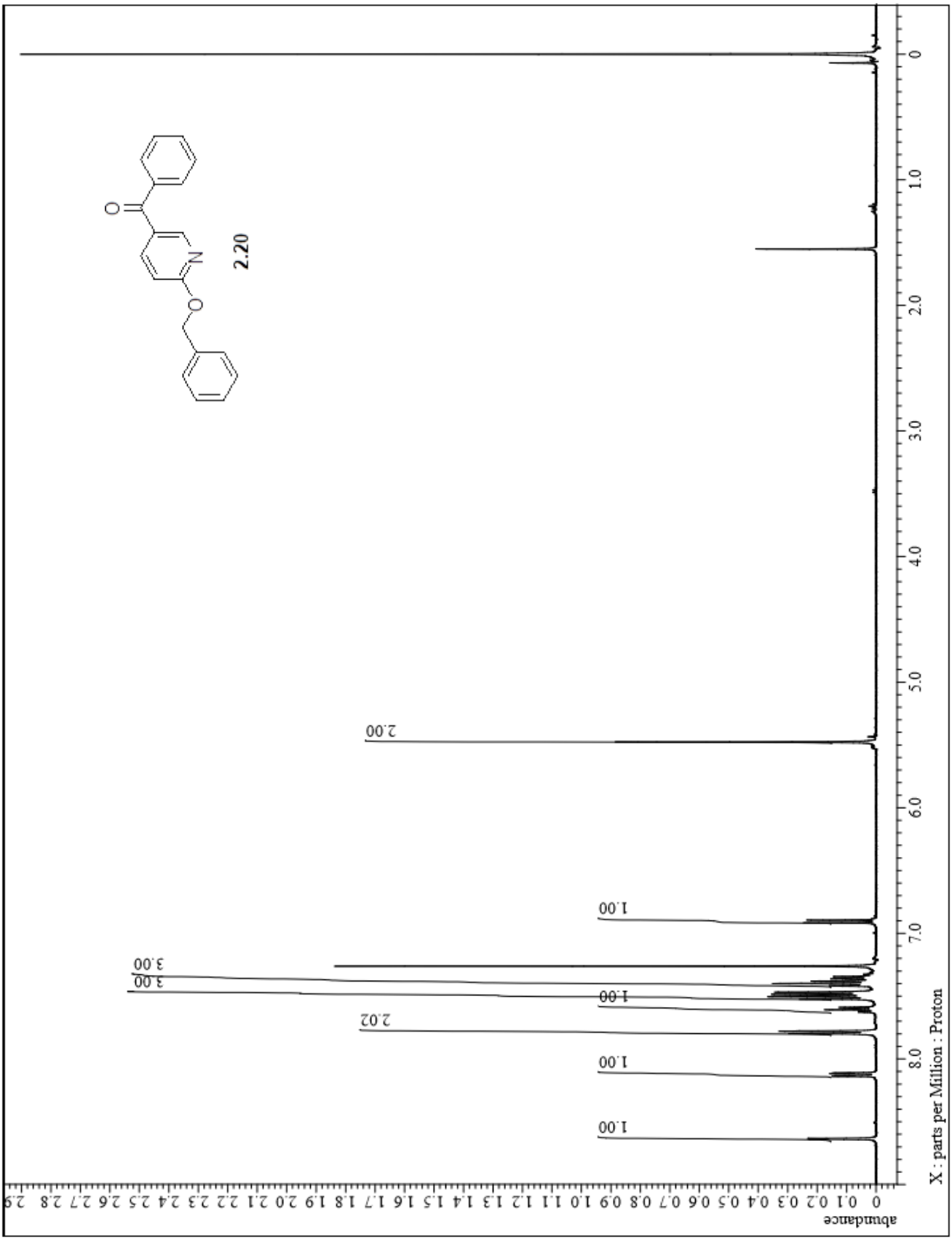
2226.68cm-1, 68.90%T
1947.24cm-1, 89.39%T
1650.67cm-1, 86.80%T
1361.80cm-1, 52.71%T
1009.58cm-1, 47.69%T
727.19cm-1, 31.95%T
%T
2.17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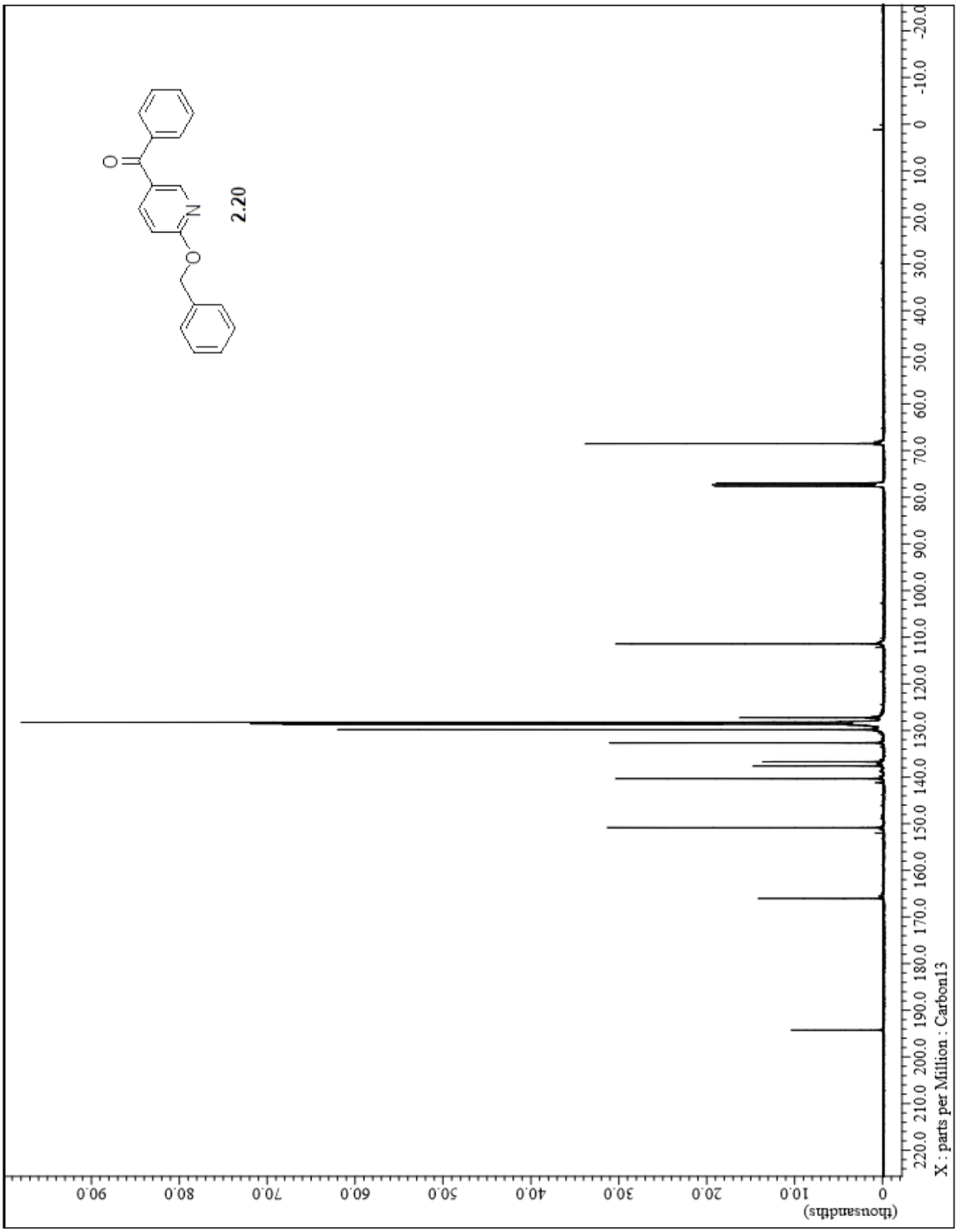
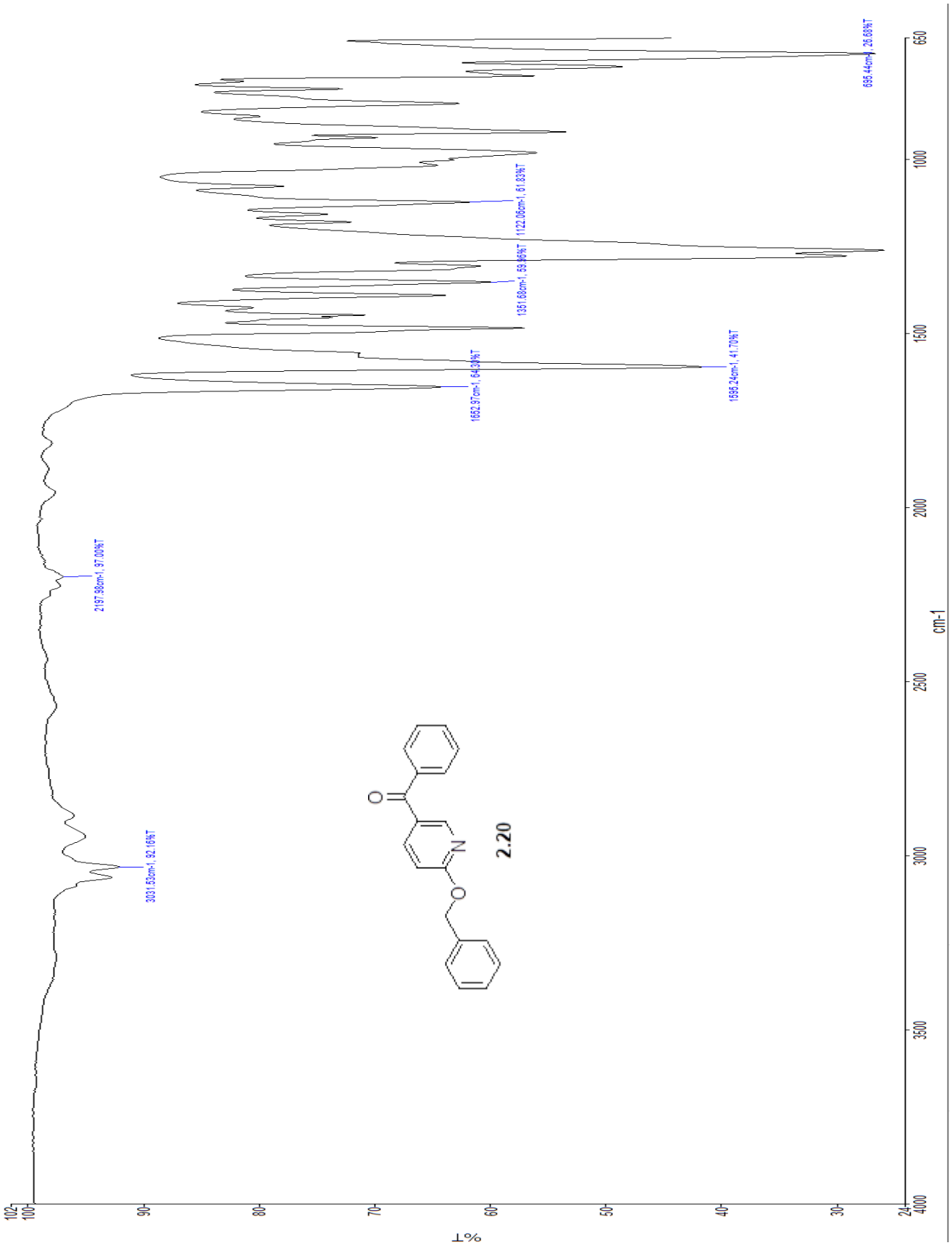
X : parts per Million : Proton
abundance


O
N
O
2.20
X : parts per Million : Carbon13
(thousandths)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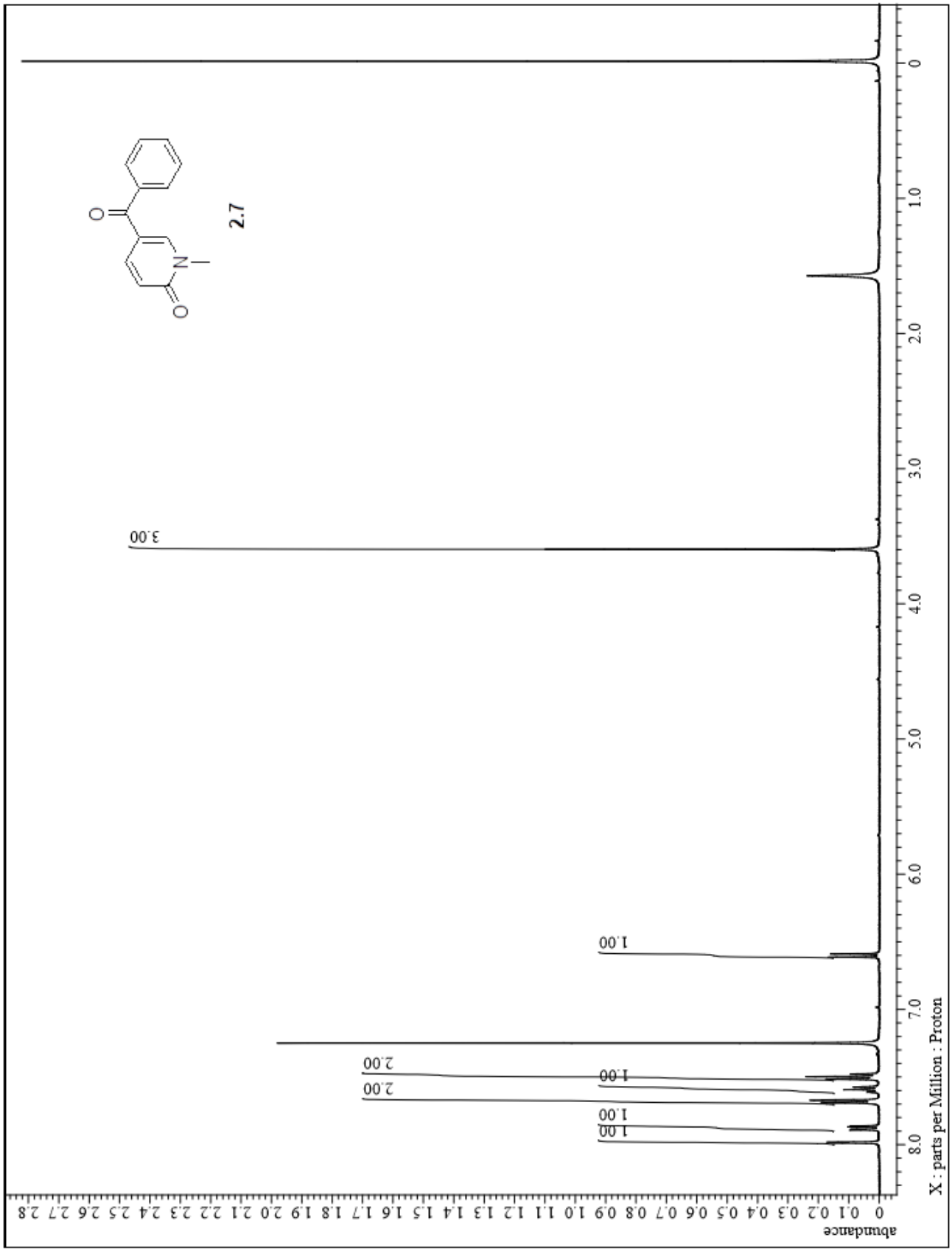
1595.24cm-1, 41.70%T
1351.68cm-1, 59.86%T
1122.06cm-1, 61.83%T
695.44cm-1, 26.68%T
O
N
O
2.20
%T
cm-1

Appendices B: Supporting Information for the Isolated Compounds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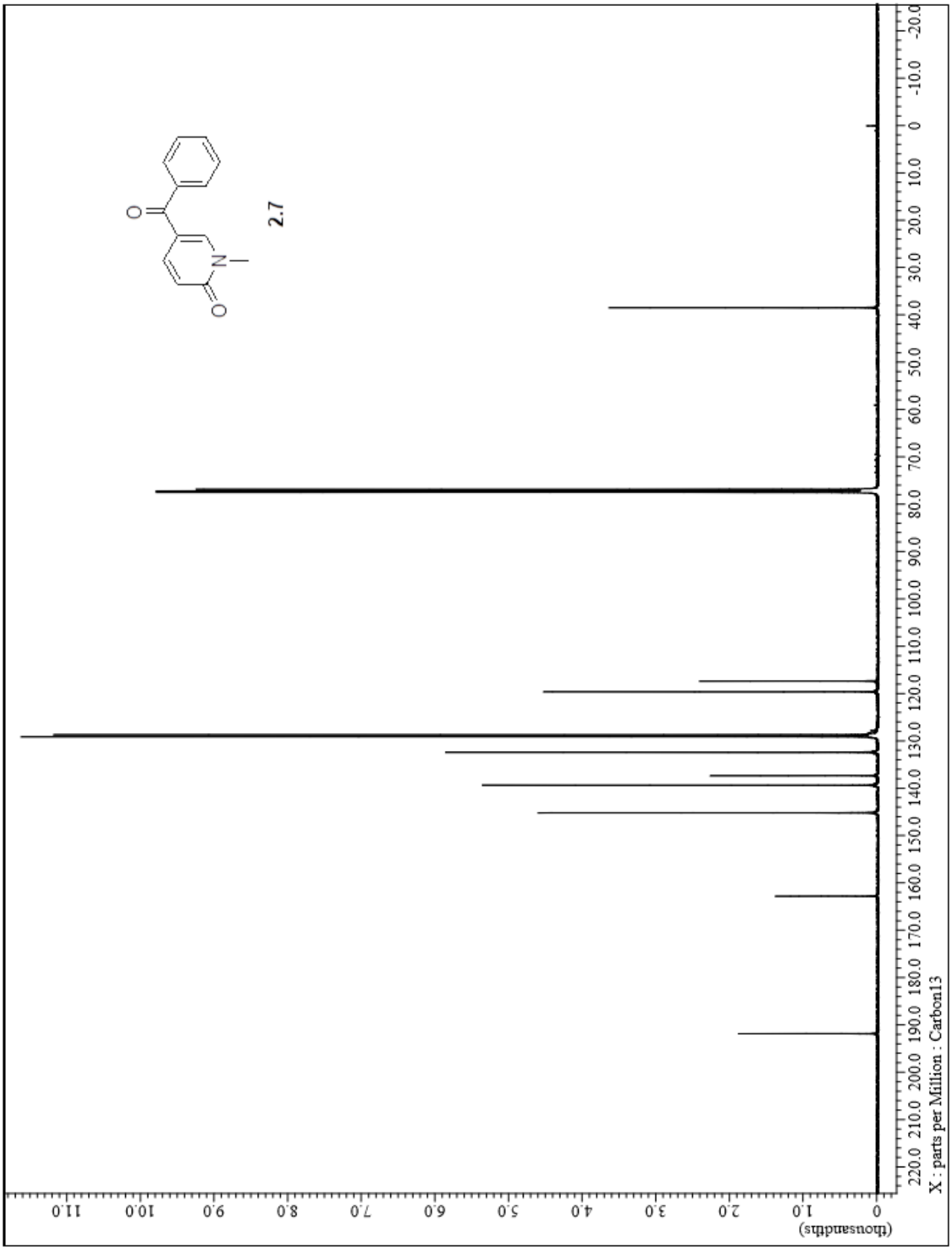
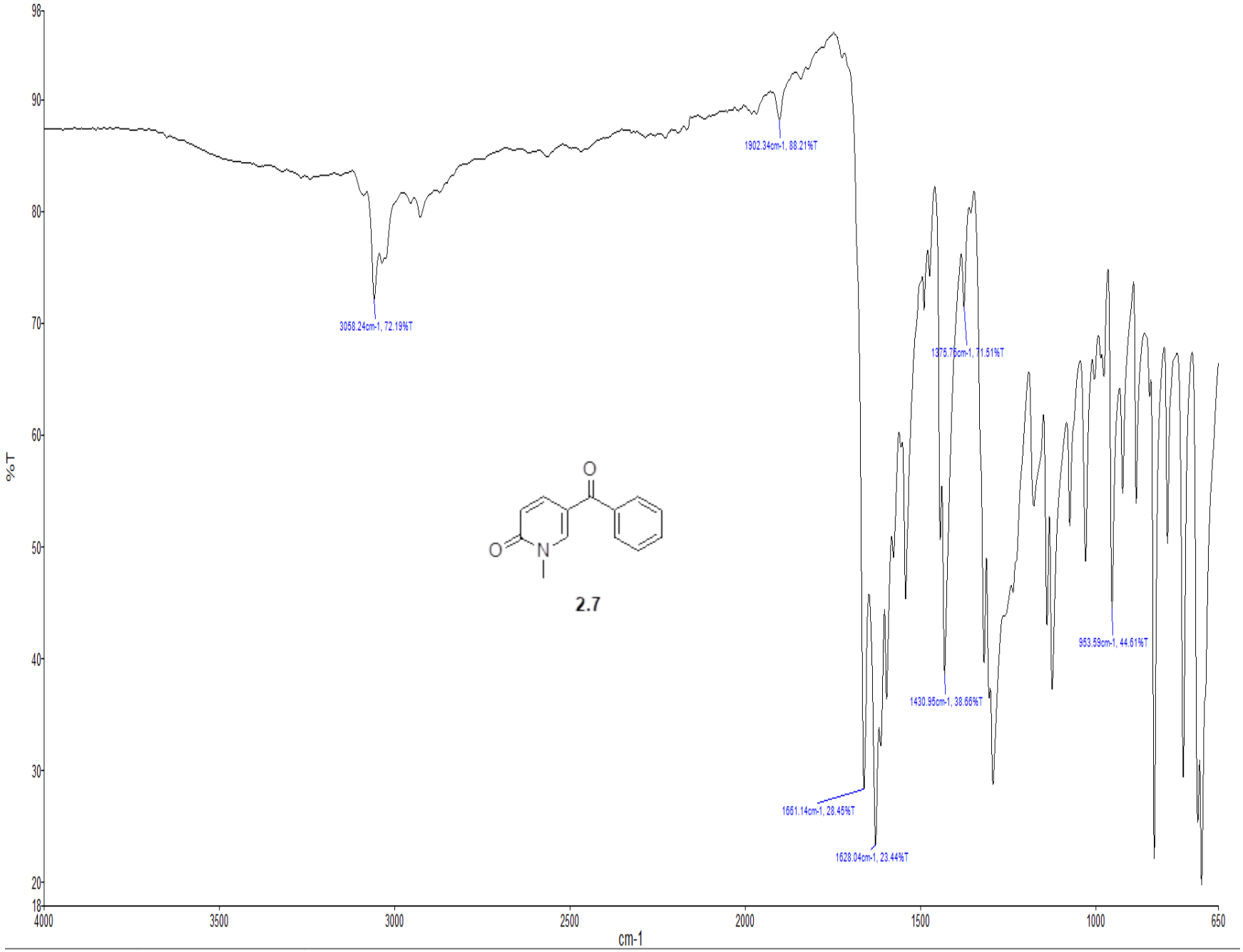
2.00
1.00
1.00
2.00
1.00
X : parts per Million : Proton
abundance


O
N
O
2.7
(thousandths)
X : parts per Million : Carbon13

A25


%T
cm-1
3058.24cm-1, 72.19%T
1902.34cm-1, 88.21%T
1661.14cm-1, 28.45%T
1628.04cm-1, 23.44%T
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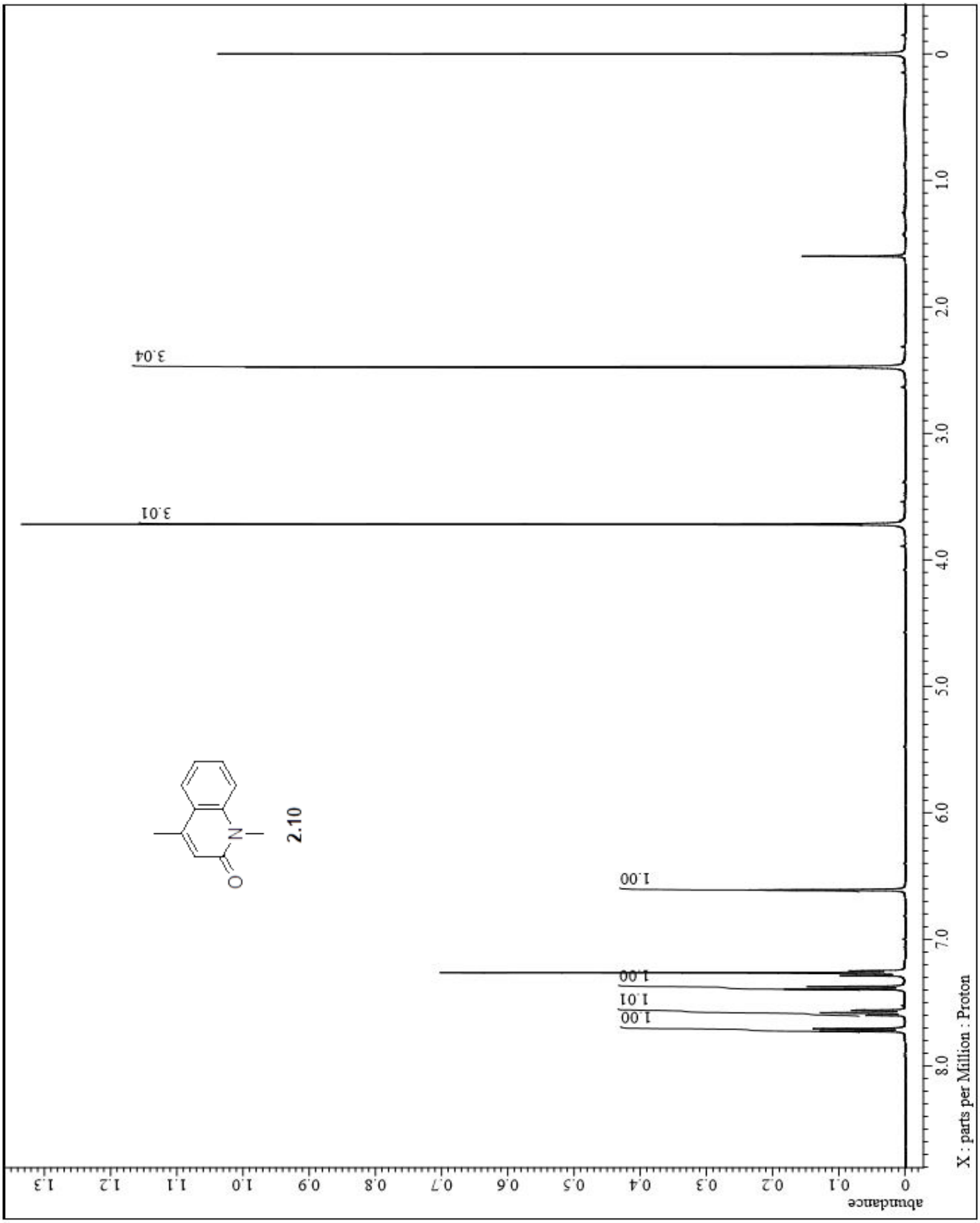
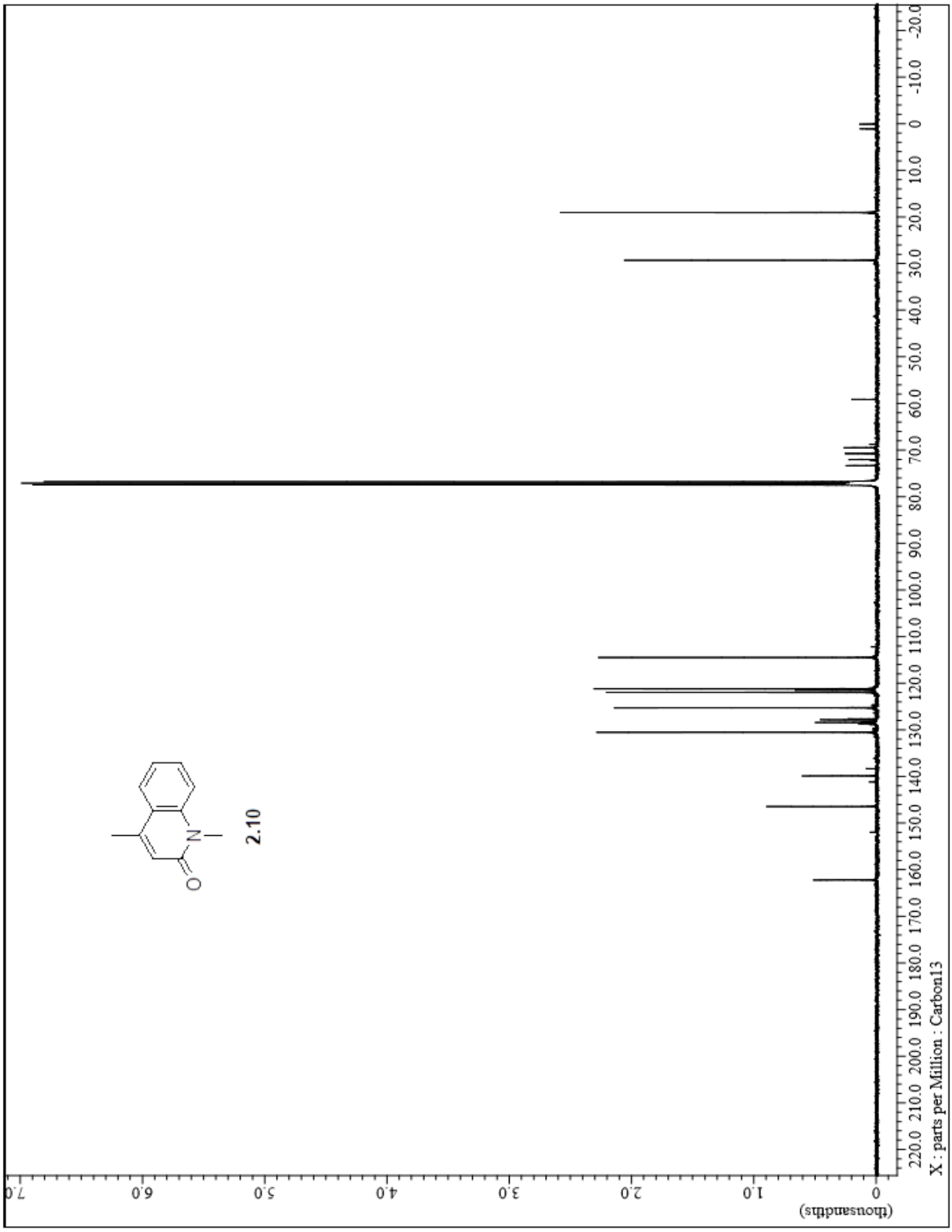
953.59cm-1, 44.61%T
2.7


2.10
3.01
3.04
1.00
1.00
1.01
1.00
X : parts per Million : Proton
abundance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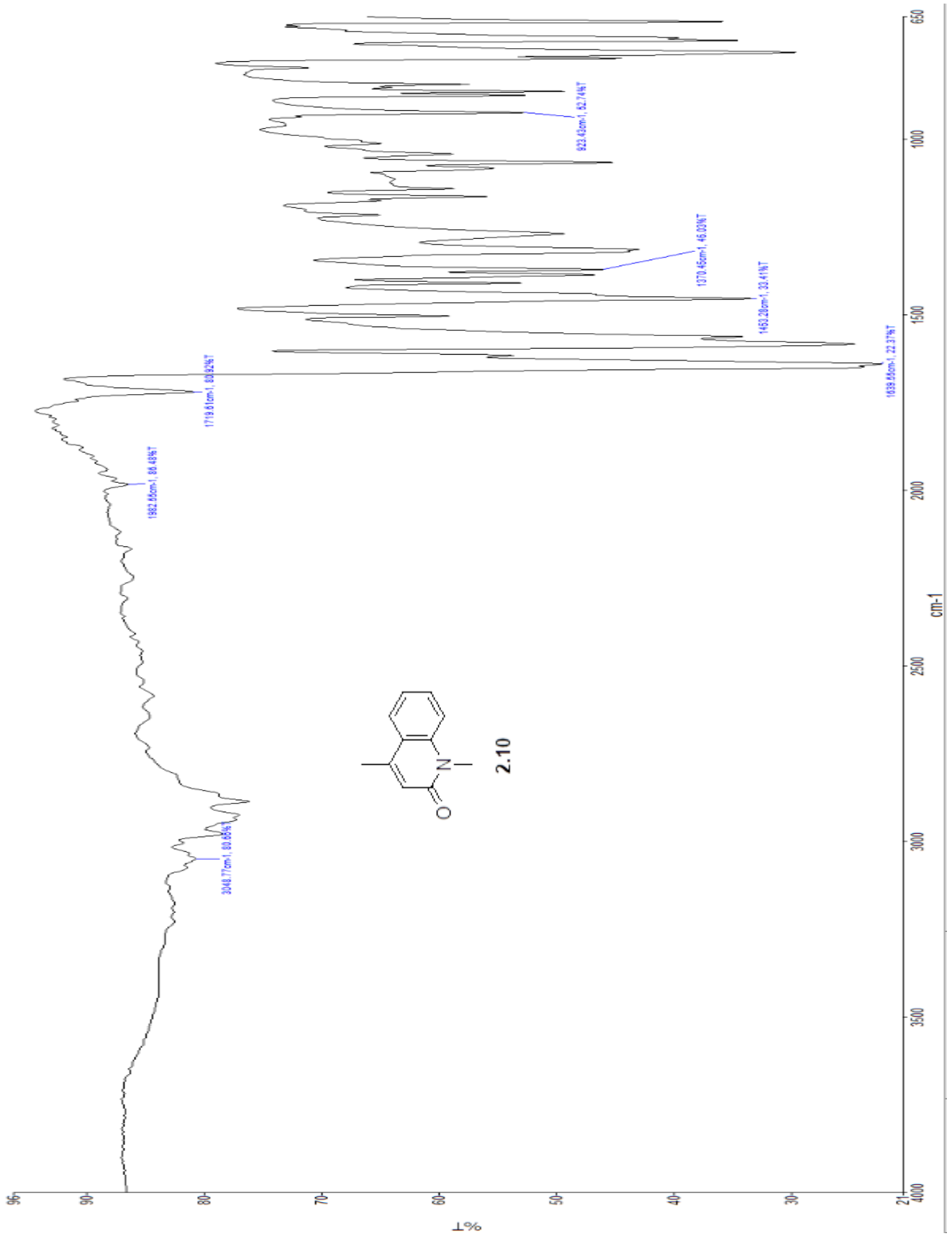
X : parts per Million : Carbon13
(thousandths)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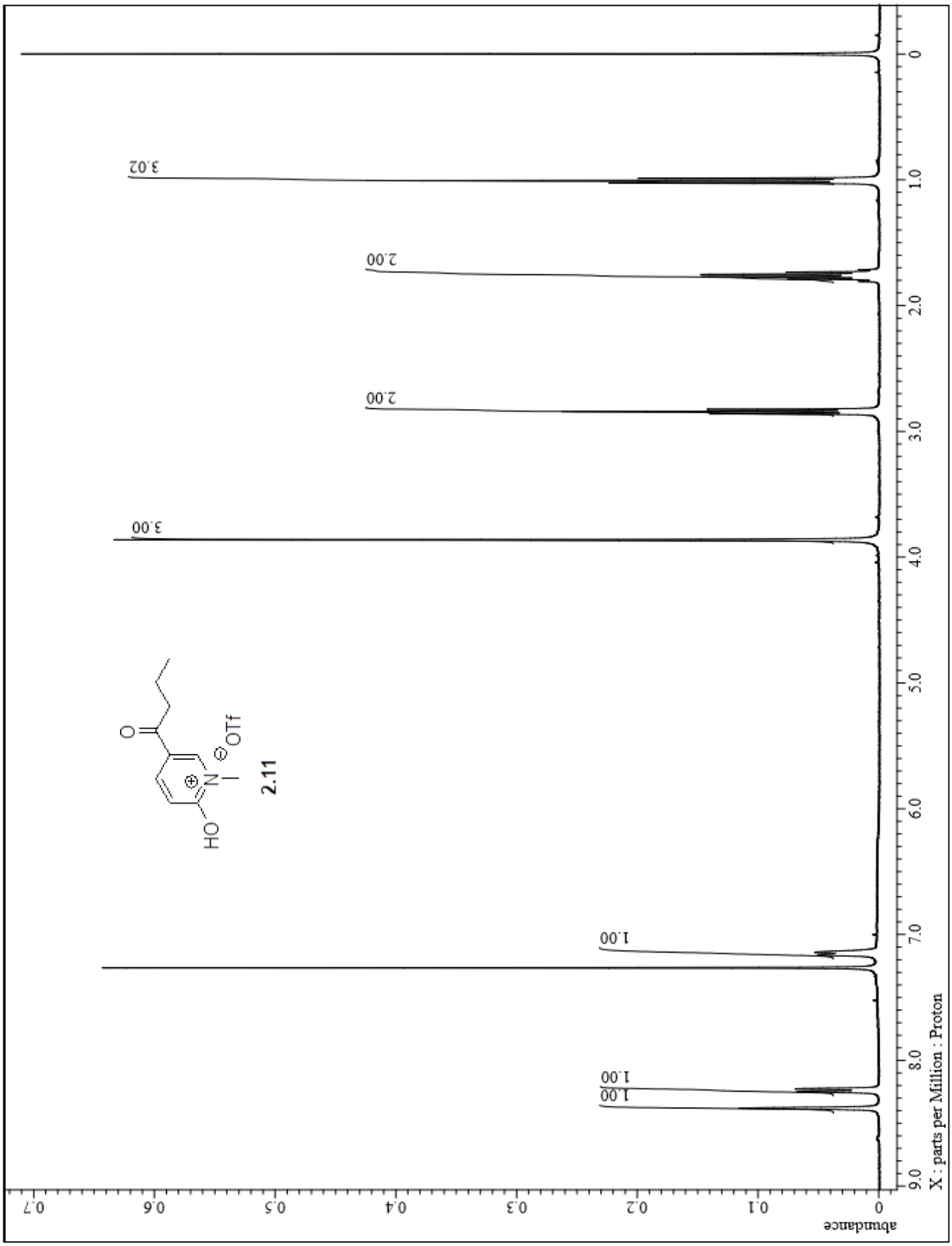
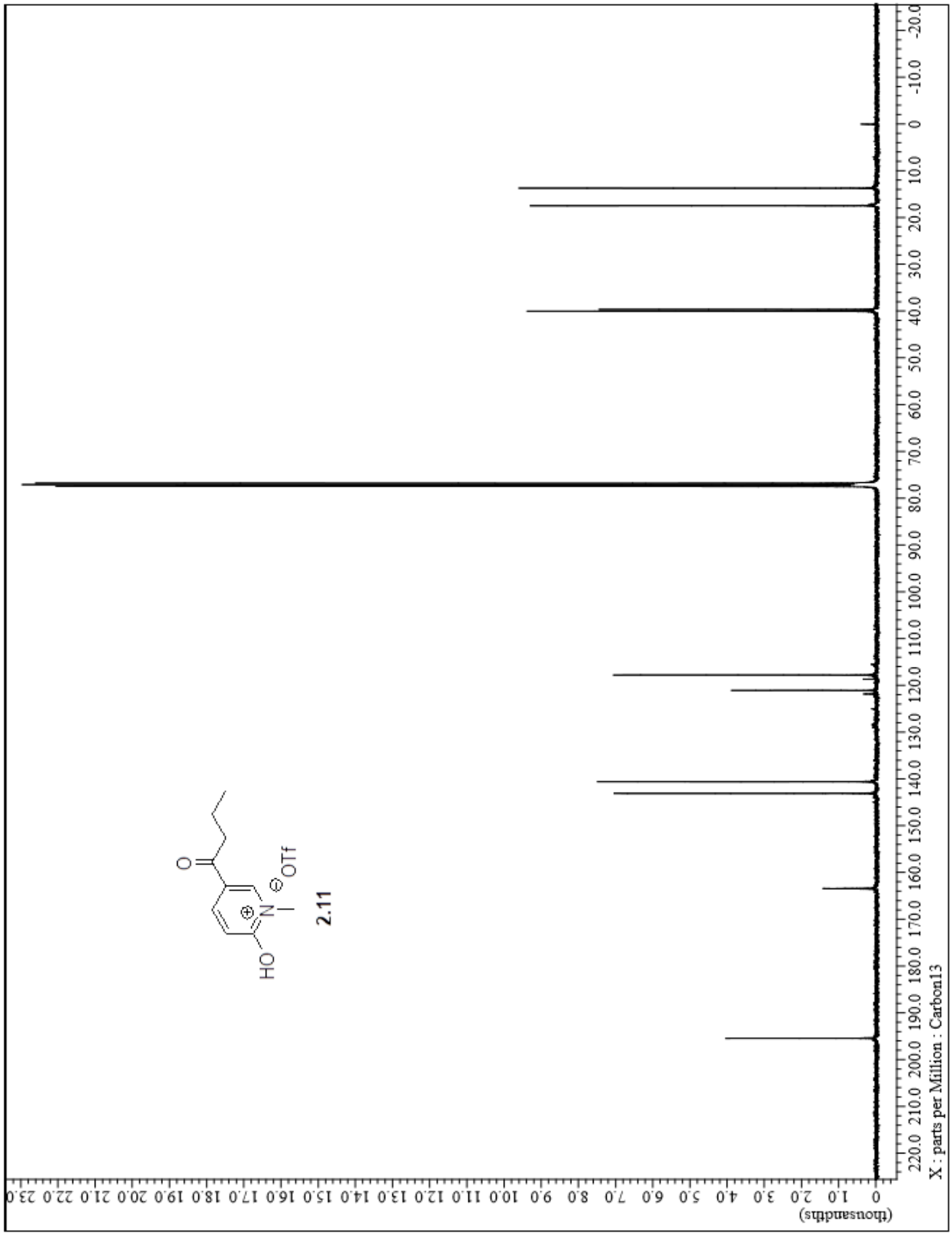
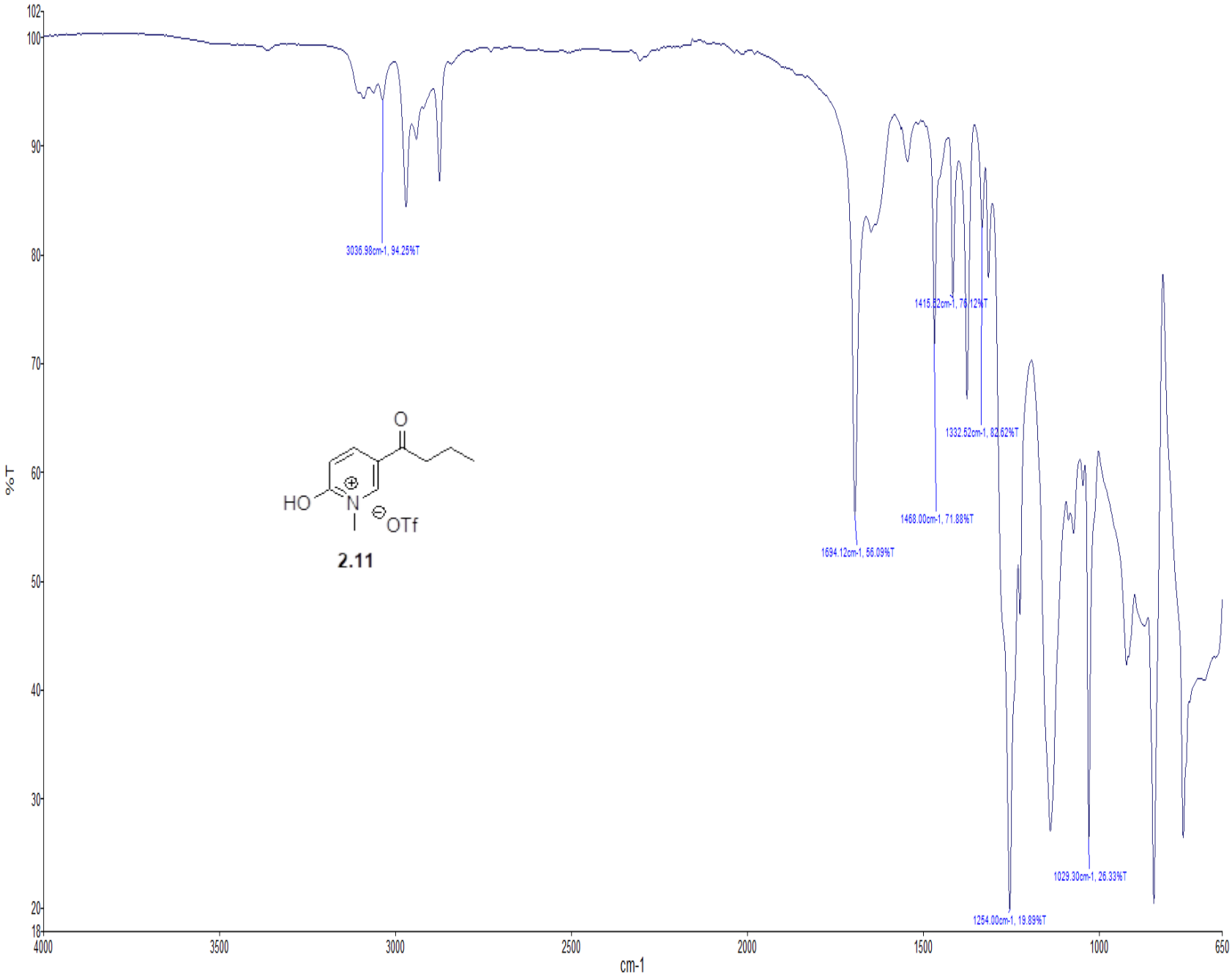
2.10
%T
cm-1


abundance
X : parts per Million : Proton
1.00
1.00
1.00
3.00
2.00
2.00
3.02
HO
N
OTf
O
2.11


(thousandths)
X : parts per Million : Carbon13
HO
N
OTf
O
2.11

A31


%T
cm-1
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1694.12cm-1, 56.09%T
1468.00cm-1, 71.88%T
1415.82cm-1, 76.12%T
1332.52cm-1, 82.62%T
1254.00cm-1, 19.89%T
1029.30cm-1, 26.33%T
HO
N
OTf
O

2.11